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In association with the British Cardiac Society

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BRITISH HEART JOURNAL

In association with the British Cardiac Society
A Registered Charity

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CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

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All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

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Br Heart J 1991,65:1

BRITISH
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Editorial

Style and substance: further improvements

A year ago the *British Heart Journal* made important changes to its appearance and at the same time introduced more variation into its contents, which were expanded to include new sections on technology, news about the British Cardiac Society, historical vignettes, and reviews of selected books.[1] The larger format, enhanced quality of illustrations, and altered layout gave greater flexibility in presenting material; and the response from readers has been favourable.

More informative abstracts

But change is not something done in one fell swoop. Now that these modifications have been tested we will continue the process. Our wish to have structured abstracts[2] will be implemented and advice on how to prepare them is reprinted below. We have extracted our guidelines on structured abstracts from a recent paper in the *Annals of Internal Medicine*.[3] The detailed headings—Objective, Design, Setting, Patients (Participants), Interventions, Main outcome measures, Results, Conclusions—cannot be applied to all papers, but where they can we propose to use them as a framework for organisation and will not necessarily print the headings. Some of the headings, such as "Setting", use terms more suited to North American practice, and the local equivalent reflecting the background of the author(s) and their work will be acceptable; so, too, will the recommendations of the *New England Journal of Medicine*, which are to specify Background, Methods, Results, and Conclusions, sometimes combining two of the first three headings, when appropriate.[4]

We will welcome all submitted articles that use this format, but the change will be a progressive one that we plan to implement during 1991. Some articles are already in the press, so no immediate change is possible. But new articles should now be submitted with "more informative abstracts". Should articles already with us need to be returned to authors for amendment, we will ask for the abstract to be rewritten. We expect that in the second volume of the *British Heart Journal* for 1991 the abstracts in the new style will prevail.

Avoiding duplicate publication

Like the *British Medical Journal*, our publishers,[5] we want to avoid repetitive publication. The problems that this raises are restated clearly by the new editors of the *Annals of Internal Medicine*, whose views are well worth reading.[6] We urge authors who are in doubt about previous letters or papers they may have written on the same topic to raise this point in the covering letter, when they submit their paper, so that we can offer advice at an early stage.

We beg to differ with those who think that these matters are of editorial concern only. Specialty journals, such as the *British Heart Journal*, are often edited by part time editors who are also authors themselves. That our interests are mutual is set out most clearly in a perceptive analysis of the role of the medical author by Fye, a distinguished practising cardiologist who is also renowned for his literary and historical accomplishments.[7] All will endorse his hope that "growing awareness of the problems of the 'publish or perish' ethic" will enable us to achieve the aim that "quality rather than quantity will be the bench mark of success". The changes that we are now implementing are directed towards this goal and will be followed by other journals; readers and authors should be reassured that we are constantly seeking ways by which we can enhance the quality of the *British Heart Journal*.

DENNIS M KRIKLER

Editor

1 Krikler DM, Dawson J. British Heart Journal: content . . . and style. *Br Heart J* 1990,63:1–2.
2 Lock S. Structured abstracts. *Br Med J* 1988;297 156.
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4 Relman AS. New "information for authors"—and readers. *N Engl J Med* 1990,323·56.
5 Lock S. Publication: duplicate, salami, meat extender—all redundant. *Br Med J* 1989;298·1203–4.
6 The editors. Policy on repetitive publication and copyright. Annals of Internal Medicine. *Ann Intern Med* 1990;113:182.
7 Fye WB. Medical authorship traditions, trends and tribulations. *Ann Intern Med* 1990,113:317–25

Abbreviated instructions for authors on structured abstracts

Articles containing original data concerning the course (prognosis), cause (aetiology), diagnosis, treatment, prevention, or economic analysis of a clinical disorder or an intervention to improve the quality of health care should include a structured abstract of no longer than 250 words with the following headings and information:

Objective State the main question or objective of the study and the major hypothesis tested, if any.

Design: Describe the design of the study indicating, as appropriate, use of randomisation, blinding, criterion standards for diagnostic tests, temporal direction (retrospective or prospective), and so on.

Setting: Indicate the study setting, including the level of clinical care (for example, primary or tertiary, private practice or institutional).

Patients, Participants· State selection procedures, entry criteria, and numbers of participants entering and finishing the study.

Interventions. Describe the essential features of any interventions, including their method and duration of administration.

Main Outcome Measure(s): The primary study outcome measures should be indicated as planned before data collection began. If the hypothesis being reported was formulated during or after data collection, this fact should be clearly stated

Results: Describe measurements that are not evident from the nature of the main results and indicate any blinding. If possible, the results should be accompanied by confidence intervals (most often the 95% interval) and the exact level of statistical significance. For comparative studies confidence intervals should relate to the differences between groups. Absolute values should be indicated when risk changes or effect sizes are given.

Conclusions. State only those conclusions of the study that are directly supported by data, along with their clinical application (avoiding overgeneralisation) or whether additional study is required before the information should be used in usual clinical settings. Equal emphasis must be given to positive and negative findings of equal scientific merit.

Abstracts for review articles should have the following headings and information:

Objective: State the primary objective of the review article.

Data Sources: Describe the data sources that were searched, including dates, terms, and constraints.

Study Selection: Identify the number of studies reviewed and the criteria used for their selection.

Data Extraction. Summarise guidelines used for abstracting data and how they were applied.

Data Synthesis: State the main results of the review and the methods used to obtain these results.

Conclusions· State primary conclusions and their clinical applications, avoiding overgeneralisation Suggest areas for additional research if needed (Further details can be obtained from: Haynes RB, *et al.* More informative abstracts revisited. *Ann Intern Med* 1990;113.69–76.)

Br Heart J 1991;65:2-3

Editorial

Lipoprotein (a): a possible link between lipoprotein metabolism and thrombosis

Lipoprotein (a) was first described in 1963 by Kare Berg. It was initially considered to be a qualitative genetic marker but has subsequently been shown to be a quantitative trait. The concentration of lipoprotein (a) can vary enormously between different individuals. Epidemiological studies typically show a highly skewed distribution within a population, with most individuals having low concentrations of lipoprotein (a). Much of the interest in lipoprotein (a) stems from several clinical studies that showed a highly significant association between raised concentrations of lipoprotein (a) and susceptibility to coronary artery disease. Angiographic studies suggest that the concentration of lipoprotein (a) is a risk factor for disease in both native coronary vessels and saphenous vein bypass grafts.[1] In addition, lipoprotein (a) immunoreactive material has been identified in the endothelium and intima of atherosclerotic coronary arteries.

Though lipoprotein (a) was characterised in some detail in the 1970s, interest in its structure-function relations has intensified recently. Essentially, lipoprotein (a) is a low density lipoprotein (LDL) particle that has been modified by the binding of a unique high molecular mass glycoprotein called apolipoprotein (a) to apolipoprotein B, the sole protein constituent of LDL. This macromolecular complex is known as lipoprotein (a) (fig 1). Lipoprotein (a) concentrations vary considerably between individuals and it is the only major lipid risk factor with a concentration that is only slightly influenced by metabolic, endocrine, or anthropometric variables—so it remains remarkably constant within an individual. The most popular hypothesis is that a single autosomal genetic locus is the major determinant of lipoprotein (a) concentration.[2] The evidence points to this locus being the gene encoding for apolipoprotein (a) itself. Apolipoprotein (a) has been shown to exist as several different isoforms—distinguished by size and mobility on gel electrophoresis. Such phenotypic variation is thought to reflect allelic polymorphisms at the apolipoprotein (a) gene locus. These allelic variants have, in turn, provided new insights into the genetics of the quantitative lipoprotein (a) trait. At least six allelic variants have been identified and an operational "null" allele postulated. There is a strong inverse relation between the mass of the differing apolipoprotein (a) isoforms and the plasma lipoprotein (a) concentrations. Thus alleles encoding for the separate apolipoprotein (a) phenotypes strongly influence the lipoprotein (a) concentration, and in individuals with the operational "null" allele lipoprotein (a) concentrations are low.

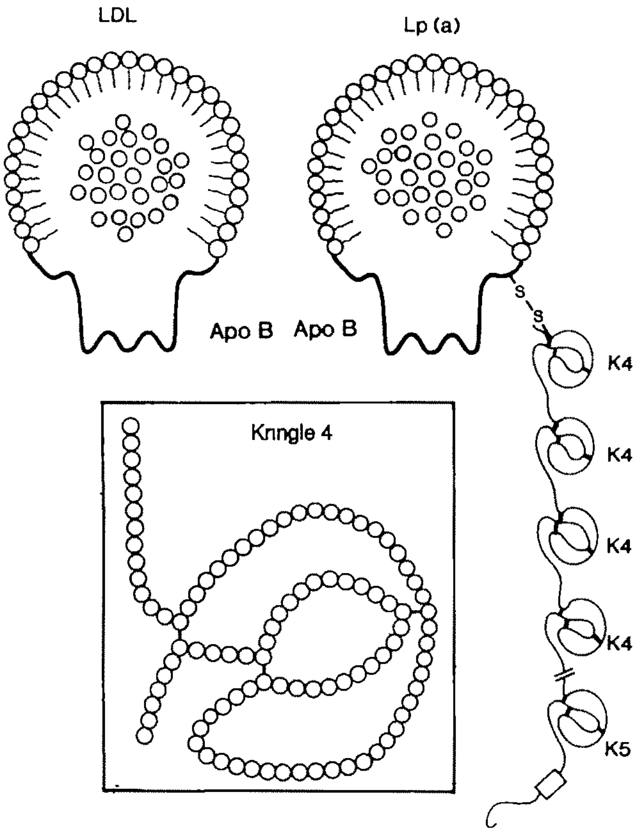

Figure 1 Structure of low density lipoprotein (LDL) and lipoprotein (a) (Lp(a)). Lipoprotein (a) is essentially an LDL particle modified by the binding of apolipoprotein (a) (apo(a)) via a disulphide bridge to apolipoprotein B. [Inset] Pretzel-like structure of the kringle 4 domain in apolipoprotein (a).

Interest in this topic was greatly stimulated by McLean *et al*.[3] They reported the cloning and sequencing of the apolipoprotein (a) gene. The complete primary aminoacid sequence of apolipoprotein (a) was derived from the sequenced human apolipoprotein (a) cDNA and it showed a striking homology to the structure of plasminogen—the zymogen of the fibrinolytic enzyme plasmin. Plasminogen is a single chain protein of 791 aminoacids containing several distinct structural regions. These include an N-terminal sequence, followed by five tandemly repeated domains called kringles, each showing about 50% homology to each other, followed by a trypsin-like protease domain. The kringles are pretzel-shaped structures, stabilised by three internal disulphide bridges and are so called because they resemble a Danish cake called a kringle (fig 1 (inset)). The primary sequence of apolipoprotein (a) also contains an N-terminal sequence one copy of plasminogen's fifth kringle and a variable copy number of the fourth kringle domain followed by a serine protease domain all of which show a high degree of homology to the equivalent regions in the plasminogen gene. In the apolipoprotein (a) cDNA sequenced by McLean *et al* there were 37 copies of the fourth kringle domain (fig 2). However, despite apolipoprotein (a) retaining a highly conserved serine protease domain, no latent enzymatic activity can be generated because of a crucial serine for arginine substitution at the homologous activation site.

The presence of regions of duplicated sequence retaining 100% identity within the gene suggests frequent expansion and contraction at the locus. Thus, it is possible that homologous recombination events that add or eliminate certain domains (for example kringle IV domains) at this locus are probably still occurring. This mechanism may well explain both the allelic variation at the apolipoprotein

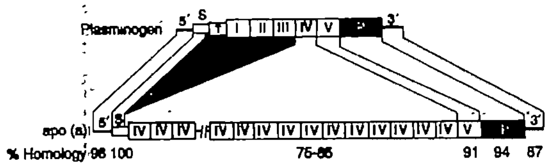

Figure 2 Comparison of the gene structures of plasminogen and apolipoprotein (a) (apo(a)). The top structure is plasminogen cDNA and the lower structure apolipoprotein (a) cDNA. Connecting lines indicate regions of homology with percentage identity between the two sequences shown at the bottom. (This illustration is derived from reference 3.) 5', 5' untranslated sequence; S, signal peptide; T, "tail" region; I, II, III, IV, V, kringle domains; P, protease domain; 3', 3' untranslated sequence.

(a) locus and the size variation of apolipoprotein (a) among individuals. Expression of the larger apolipoprotein (a) alleles may test the limits of the translation and transcription machinery of the cell, by mechanisms such as messenger RNA instability, decreased transcription efficiency, etc. This accords with the inverse correlation between lipoprotein (a) concentrations and the size of the apolipoprotein (a) isoforms.

In general, the kringle domains serve as regulatory domains and are important for the activation of specific proteases such as plasminogen and tissue plasminogen activator. Thus, there has been considerable speculation that lipoprotein (a) may interfere with the fibrinolytic system because of its structural homology to plasminogen. In vitro data supporting this hypothesis are beginning to accumulate. Lipoprotein (a) has been shown to inhibit binding of plasminogen to its endothelial cell binding sites with a consequent reduction in generation of plasmin by tissue plasminogen activator. Lipoprotein (a) has also been shown to compete with both plasminogen and tissue plasminogen activator for fibrin binding and it attenuates both the fibrin dependent enhancement of tissue-type plasminogen activator activity and clot lysis in vitro.[4] Confirmation of these effects in vivo would demonstrate that lipoprotein (a) is a vital link between lipoprotein metabolism and the thrombolytic system.

Little is known about the synthesis and catabolism of lipoprotein (a). Circumstantial evidence suggests it is synthesised by the liver because the apolipoprotein (a) cDNA was constructed from a library of hepatic RNAs. This accords with the low concentration of lipoprotein (a) in individuals with chronic hepatic disease such as cirrhosis. While lipoprotein (a) concentrations are thought to be largely determined by the apolipoprotein (a) gene locus, other gene loci may also be influential in determining concentrations. One such locus is the LDL receptor locus. There are discrepant and conflicting data about the in vitro binding and uptake of lipoprotein (a) by the LDL receptor. However, it has been shown in vivo that irrespective of apolipoprotein (a) phenotype, patients heterozygous for familial hypercholesterolaemia, a disease caused by defective LDL receptor function, have lipoprotein (a) concentrations 2·5 to three times higher than age and sex matched controls.[5] In patients with familial hypercholesterolaemia there is a 10 fold increase in the risk of coronary heart disease. In such a relatively homogeneous, monogenic disease, however, the expression of this susceptibility varies between individuals and particularly between families with the condition. Some of the variability may be explained by the finding of two recent reports from London and Sweden.[6,7] In both, over 100 patients with familial hypercholesterolaemia were subdivided on the basis of the presence or absence of clinically documented coronary heart disease. While the LDL cholesterol concentrations were equivalent in both subgroups, patients with coronary heart disease had significantly higher lipoprotein (a) concentrations and this value was the best discriminant for the presence of coronary heart disease on both univariate and multivariate analysis. These findings have important implications for both the management and prognosis of familial hypercholesterolaemia. Indeed, they may reveal an oversimplification in the treatments designed for the hyperlipidaemias in general. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, the fibric acid derivatives, and the ion-exchange resins do not significantly alter lipoprotein (a) concentrations. To date, only nicotinic acid, neomycin, and extracorporeal apheresis have been effective in reducing lipoprotein (a) concentrations. Each of these treatments has drawbacks. Furthermore, there are no published data to show any benefit in lowering lipoprotein (a) concentrations in individual patients.

Should measurement of lipoprotein (a) concentration become part of the full lipid profile and would concomitant reduction of lipoprotein (a) and LDL cholesterol concentrations have a synergistic effect on the reduction of the risk of coronary artery disease in familial hypercholesterolaemia and the hyperlipidaemias in general? Risk reduction is being studied by a two centre trial based at the Royal Postgraduate Medical School, Hammersmith, and the University Hospital of Wales, Cardiff. This trial is designed to assess whether LDL apheresis (which lowers both lipoprotein (a) and LDL cholesterol) is more beneficial in patients with familial hypercholesterolaemia than drug treatment (which does not reduce lipoprotein (a) concentrations). It is too early to recommend the routine measurement of lipoprotein (a) concentrations. Lipoprotein (a) assays need to be standardised and fully characterised to allow appropriate interpretation. An international standardisation programme is evolving. While measurement of lipoprotein (a) is likely to be more expensive than a basic lipid profile, the rationale for measuring risk factors is to estimate the risk of developing coronary artery disease. The current controversy about the precise concentrations of cholesterol at which hypolipidaemic drug treatment should be started, and the possible role of high concentrations of lipoprotein (a) in altering the thrombotic/fibrinolytic equilibrium suggest to me that lipoprotein (a) measurements will be widely available in clinical practice within the next decade.

An understanding of the role of lipoprotein (a) in atherogenesis, evaluation of the apparent synergy between lipoprotein (a) and LDL cholesterol in promoting coronary artery disease, and the assessment of the therapeutic benefits of reducing lipoprotein (a) in specific patient groups should yield results soon.

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Br Heart J 1991;65:4–8

ORIGINAL ARTICLES

Ventricular arrhythmias during treatment with alteplase (recombinant tissue plasminogen activator) in suspected acute myocardial infarction

R G Wilcox, Janet Eastgate, Elizabeth Harrison, A M Skene

Abstract

Continuous electrocardiography during the first 24 hours of a stay in a coronary care unit was used to record ventricular arrhythmias during treatment with alteplase (recombinant tissue plasminogen activator) or placebo. Recordings were made on 378 of the 436 patients admitted to a double blind trial of alteplase or placebo in one participating centre of the Anglo-Scandinavian study of early thrombosis (ASSET), patients being selected according to the availability of recorders. Of these, 309 (158 given alteplase and 151 placebo) had >5 hours of analysable data. Most of the arrhythmias were recorded in patients with an in hospital diagnosis of myocardial infarction. Ventricular couplets and venricular tachycardia were significantly more common in the patients treated with alteplase. Further, in patients with myocardial infarction who had ventricular extrasystoles, couplets, or ventricular tachycardia type a, the number of hours in which each arrhythmia was recorded was significantly higher in the alteplase group. The various ventricular arrhythmias in the alteplase group tended to cluster in the first 4–12 hours of the recordings. During the first 24 hours admission there were four episodes of ventricular fibrillation in the alteplase group and five in the placebo group of taped patients. By one month there had been 18 deaths in these 309 patients (alteplase four, placebo 14). These bore no relation to any recorded arrhythmia. Clinical records for the patients with no or minimal tape data yielded six further episodes of ventricular fibrillation during the first 24 hours (three in the alteplase group and three in the placebo group). Of the total 436 patients, 10 of the 218 patients in the alteplase group had died by one month compared with 22 of the 218 patients treated with placebo.

The use of alteplase increases the incidence of non-life threatening ventricular arrhythmias. These results, however, suggest that arrhythmia after thrombolysis in the pre-hospital phase may be less of a problem than it is perceived to be.

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Coronary thrombolysis is now an accepted treatment for eligible patients who present within 6 hours of onset of symptoms of acute myocardial infarction and the risk-benefit ratio of such treatment is gradually emerging from several large clinical trials.[1–4] One particular concern, especially in the pre-hospital setting, is the likelihood of such treatment provoking serious ventricular arrhythmias. In animal studies, for instance, both the occlusion of a coronary artery and its reperfusion are usually accompanied by a burst of ventricular extrasystoles that occasionally degenerates into ventricular fibrillation.[5–7] Incomplete reperfusion seems to be particularly provocative.[8]

In humans ventricular extrasystoles coincided with angiographically proven coronary artery reperfusion,[9] but in none of the large clinical trials does there seem to be an increase in serious ventricular arrhythmias during hospital stay. The data available during the operative hours of thrombolysis (and presumed reperfusion) are less complete with most of the human data coming from studies that used intracoronary or intravenous streptokinase as the thrombolytic agent. Although ventricular extrasystoles are common and cannot be prevented by lignocaine, serious events are not.[10 11] In the placebo controlled intravenous streptokinase in acute myocardial infarction (ISAM) and Gruppo Italiano per lo Studio della streptochinasi nell 'infarto miocardico (GISSI-1) trials, observation periods of cardiac rhythm were limited and in neither study did serious ventricular events seem to be more common in the actively treated groups.[1 12]

The extent to which alteplase (recombinant tissue plasminogen activator) is associated with ventricular arrhythmias is less clear. During the Anglo-Scandinavian study of early thrombosis (ASSET),[4] a large double blind placebo controlled study that used intravenous alteplase as the thrombolytic drug, we monitored ventricular extrasystoles in 378 patients by 24 hour continuous electrocardiographic recordings, started at admission to the coronary care unit. This paper reports the findings of that study.

Patients and methods

The protocol, methods, and principal results of ASSET have already been published.[4]

Briefly, patients of either sex, aged 18–75 years inclusive, admitted to the coronary care units within 5 hours of symptoms of acute myocardial infarction were screened for eligibility and then randomised to receive either intravenous alteplase (100 mg over 3 hours) or placebo. Both groups also received an initial intravenous bolus of heparin 5000 units followed by an intravenous infusion of 1000 units per hour starting after completion of the trial infusion and continuing for the remainder of the patients' first 24 hours stay in the coronary care unit. During this time no other routine or prophylactic treatments were given and it was not the policy to prescribe antiarrhythmic medication for episodes of symptomless ventricular extrasystoles.

All patients in ASSET admitted to the University Hospital, Nottingham, had continuous bedside and central console single channel electrocardiographic monitoring (Simonsen and Weel 8000 series) for the duration of their stay in the coronary care unit. In addition, a continuous recording was made during the first 24 hours on to Oxford Medilog 1 tapes from the central console via a voltage attenuator, beginning as soon as possible after clinical evaluation and randomisation. A recording was attempted whenever a tape recorder was available. Data were obtained for 378 patients from 436 study admissions.

The 24 hour tapes were then analysed by an experienced technician who inspected the scan replays from an Oxford Medilog 1 tape analyser. Any equivocal episodes were re-read by one of us (RGW). We recorded the hourly incidence of the following rhythms: ventricular extrasystoles (VEs), fast and slow ventricular couplets and ventricular tachycardias, atrial fibrillation/flutter, and supraventricular tachycardia. Any episode of ventricular fibrillation, complete heart block, or asystole was also noted. Ventricular couplets and tachycardias were coded according to the description of Campbell and colleagues:[13]

Fast ventricular couplets Two consecutive ventricular extrasystoles with RR interval <500 ms.

Slow ventricular couplets As above but with RR interval ≥500 ms.

Ventricular tachycardia (a) Three or more consecutive ventricular extrasystoles with two successive cycles contained within 1000 ms; (b) as above but at least one cycle of ≤500 ms; (c) as above but with no cycle shorter than or equal to 500 ms (VTa, VTb, VTc).

Details of all relevant clinical events and treatments during the hospital stay and up to one month were noted as part of ASSET.

Two questions were investigated for each rhythm disturbance in turn: first, was there a difference between the treatments in terms of the number of patients showing the rhythm disturbance at any time during the course of the monitoring period? Secondly, among patients who had shown the arrhythmia was the frequency of its occurrence associated with treatment? This second issue was investigated in three ways. For each patient and arrhythmia we counted the number of hourly intervals in which the arrhythmia appeared (hours seen), the total number of instances of the arrhythmia over the taping period (total on tape), and the number of instances of the arrhythmia during the hour it was most prevalent (maximum frequency per hour).

Full 24 hour records were not available for all the taped patients because of administrative or technical difficulties which often resulted in all or large parts of the tape being unreadable. We elected to include in the statistical analysis only those tapes with ≥5 hours worth of recorded data, there being no indication that any imbalance was induced between the treatment groups by this selection. However, instances of ventricular fibrillation, diagnostic categorisation in hospital, and one month outcome are known for all study admissions, including both untaped patients and those patients in whom taping was unsuccessful.

STATISTICAL ANALYSIS

We used standard methods for the analysis of frequency data. Distributions of total tape frequencies and maximum frequency per hour were often highly positively skewed with the occasional patient yielding values that were one or two orders of magnitude greater than all other cases in the group. Thus for treatment comparisons we used either rank sum statistics or we examined tables of grouped data. For the tables of grouped data the generalised logistic regression models described by McCullagh,[14] were often appropriate. Medians are cited as a measure of central tendency. Distributions of the number of hours in which a particular arrhythmia was seen were more symmetrical and thus means are given for these distributions where appropriate.

Because all patients in this study were also included in the analysis of ASSET the analysis by allocated treatment group was only carried out once the ASSET database was complete and treatment codes had been released.

Results

PATIENTS

During the course of ASSET 436 patients admitted to the University Hospital, Nottingham were randomised to treatment. Tape recorders were available for 378 (82%) patients. Of these recordings 309 had ≥5 hours of analysable data (mean 21·7 hours), 11 contained some data, but were short either because of technical difficulties or early death, and 58 tapes contained no usable data because of technical problems. A total of 158 of the 309 fully analysable taped patients were treated with alteplase. The rest (151) received placebo. Nearly all (98%) of patients in both groups received the complete dose of trial material. The treatment groups were well matched for pre-admission demographic details and clinical details on admission (table 1), time from onset of symptoms to start of trial infusion and tape length (table 2), and for in hospital diagnostic

Table 1 Comparability of treatment groups on admission

	All cases		*Confirmed MI*	
	Alteplase	*Placebo*	*Alteplase*	*Placebo*
Time (h) from onset of symptoms to start of infusion.				
<2	9	9	8	6
2–3	35	39	26	34
3–4	48	45	36	31
>4	66	58	38	41
Total	158	151	108	112
Male/female	129/29	118/33	91/17	88/24
Age:				
⩽45	16	15	9	12
46–55	44	36	29	18
56–65	63	56	46	47
66–75	35	44	24	35
Previous infarct	36	41	20	28
Angina	70	53	42	35
Hypertension	28	30	18	23
Diabetes	5	6	5	4
Smoker				
No	41	38	32	27
Ex	38	41	26	32
Yes	79	72	50	53
ECG:				
Normal	36	27	9	8
Consistent with new MI	71	81	64	79
Other abnormal	51	42	33	24
Missing	0	1	0	1
Treatment with frusemide:				
None	116	114	74	80
40 mg	30	22	24	19
80 mg	11	14	9	12
+ vasodilator	1	1	1	1
Other treatment at entry				
β blocker	33	24	16	18

ECG, electrocardiograph; MI, myocardial infarction.

Table 2 Comparability of treatment groups: time intervals

	All cases		*Confirmed MI*	
	Alteplase (n)	*Placebo (n)*	*Alteplase (n)*	*Placebo (n)*
Time from infusion to start of tape				
±30 min	110	104	73	78
30–90 min	17	12	11	11
>90 min	14	13	13	9
Not known	17	22	11	14
Tape hours available for analysis:				
6–12	6	9	0	7
13–18	21	18	11	8
19–23	38	28	23	19
24	93	96	74	78

MI, myocardial infarction.

Table 3 Hospital diagnosis, 24 hour incidence of ventricular fibrillation and one month outcome in all 436 patients

	Tape available (320)				*No tape data* (116)*	
	>5 h†		*<5 h*			
	Alteplase	*Placebo*	*Alteplase*	*Placebo*	*Alteplase*	*Placebo*
Total	158	151	7	4	53	63
Dead at 1 month	4	14	1	2	5	6
Hospital diagnosis:						
MI (dead 1 month)	110 (4)	112 (14)	5 (1)	3 (2)	39 (4)	39 (5)
IHD	25	21	0	0	12	12 (1)
Others	23	18	2	1	4 (1)	10
VF ⩽24 h	4	5	0	0	3	3

*Technical problems or recorder not available.
†Group chosen for the statistical analysis of arrhythmia incidence.
IHD, ischaemic heart disease; MI, myocardial infarction, VF, ventricular fibrillation.

categorisation and one month outcome (table 3). Table 3 also gives the diagnoses and one month outcome for the 11 patients with <5 hours analysable data and the 116 patients who had no data because of technical problems or were not taped because a machine was not available.

ARRHYTHMIAS

Most of the recorded arrhythmias occurred in patients with an in hospital diagnosis of myocardial infarction. Isolated ventricular extrasystoles were very common. They were seen in 96% of patients with myocardial infarction given alteplase or placebo, in 66% of non-infarct patients who received alteplase, and in 72% of non-infarct patients who received placebo. They occurred throughout the monitoring period for a mean of 17 hours in patients with a myocardial infarction and a mean of 10 hours in the non-infarct patients. However, more complex ventricular arrhythmia was much less common in the patients without infarcts (table 4).

When patients without infarcts were excluded, the incidence of each of fast and slow couplets, ventricular tachycardia a, b, and c, and supraventricular tachycardia was significantly higher in the alteplase group. In addition, a higher proportion of alteplase patients recorded a rate for isolated ventricular extrasystoles of >30 per hour for at least one hour.

Table 5 indicates that the treatment with alteplase was also associated with a small increase in the frequency of the occurrence of most of the arrhythmias considered. Among patients with myocardial infarction and VEs, couplets, VTas, or VTcs the number of hours during which each was seen was significantly higher in the alteplase group. There was no significant increase in the maximum frequencies per hour, but the increase in the number of hours during which an arrhythmia was seen caused a corresponding increase in the total on tape.

Hourly analysis of the patient incidence of the various arrhythmias showed that the increase in the alteplase group was more considerable during the first 12 hours of the recordings. Thereafter the incidence in both groups gradually declined (fig 1A–D).

During the first 24 hours of admission there were four reports of ventricular fibrillation in the alteplase group with analysable tapes and three reports in the group of 53 alteplase patients with no tape data. There were five reports of ventricular fibrillation in the placebo group with analysable tapes and three reports from the group of 63 placebo patients with no tape data. The ventricular fibrillation episodes proved fatal for two patients—one in the alteplase group and one in the placebo group (table 3).

CLINICAL CORRELATIONS

By one month there had been 18 deaths (four in the alteplase group and 14 in the placebo group) in the analysable patients; all deaths occurred in patients who had an in hospital

Table 4 Number of patients with arrhythmias: by diagnosis and treatment

	MI		*Non-MI*	
	Alteplase (108)	*Placebo (112)*	*Alteplase (50)*	*Placebo (39)*
VE > 30/h	58	44*	9	9
Couplets:				
Fast	80	57*	5	2
Slow	76	61*	8	6
VT:				
a	68	54*	5	5
b	28	17*	1	1
c	64	46*	2	4
R on T	7	2	1	1
SVT	34	19*	5	3

MI, myocardial infarction; SVT, supraventricular tachycardia; VE, ventricular extrasystoles, VT, ventricular tachycardia.
*Data not consistent with the hypothesis of equal incidence rates in the two treatment groups, ($p < 0·05$). Separate tests for MI and non-MI groups

diagnosis of acute myocardial infarction. However, there seemed to be no relation between the arrhythmias recorded in the first 24 hours and the day on which death eventually occurred (table 6). Indeed, we explored the clinical database for possible differences between those patients who did or did not show ventricular arrhythmias and between those who died and those who survived; we could find no predictive features, such as age, site of infarct, or smoking habit. The excess incidence of recorded arrhythmias in the alteplase group occurred across the board, rather than being confined to a subset of patients.

Discussion

Early treatment with any of the currently available thrombolytic regimens has been shown unequivocally to save lives.[1-4] However, both the GISSI 1 study and the second international study of infarct survival (ISIS 2) showed that thrombolysis was accompanied by a slight excess of deaths in the first 24–48 hours in patients treated with streptokinase. Although the cause of death is not always easy to determine, we need to confirm or refute the involvement of reperfusion arrhythmias, particularly because concern has been expressed about the safety of the environment in which thrombolysis is initiated.[15]

This subset of patients from ASSET now provides specific evidence that the use of alteplase is accompanied by an increased incidence of ventricular arrhythmias. Treatment with alteplase seems to increase both the number of patients who show a range of arrhythmias and to increase slightly the frequency of the occurrence of these events.

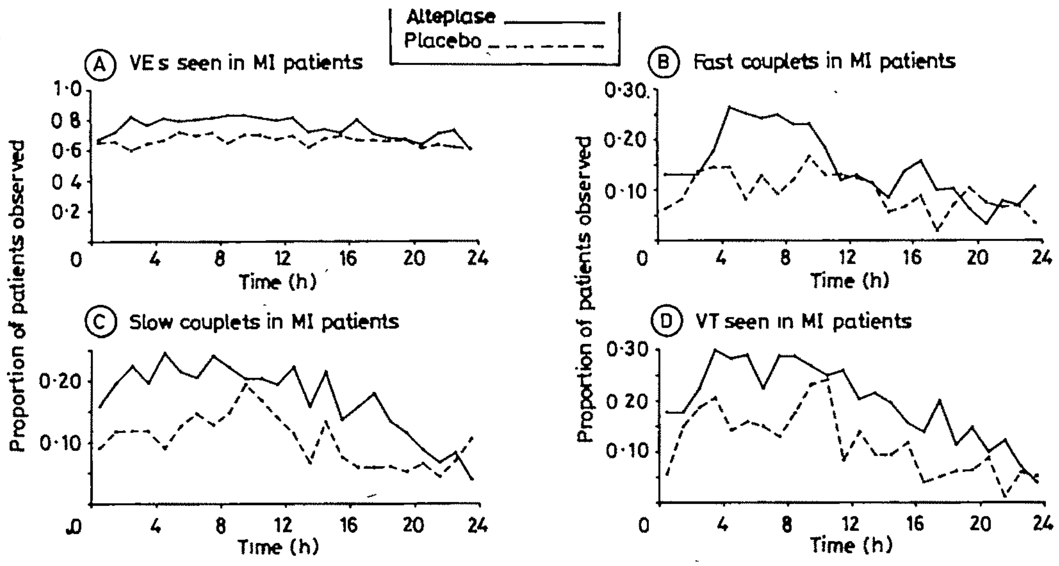
The most worrying arrhythmia, however, is ventricular fibrillation, especially if thrombolytic treatment is given before admission to hospital. In a large series from Rotterdam intracoronary streptokinase was compared with conventional treatment; a lower incidence of both early and late ventricular fibrillation was reported in the thrombolytic group.[11] Similarly in the intravenous streptokinase in acute myocardial infarction (ISAM) study there was a significantly lower incidence of late, but not early, ventricular fibrillation.[12] In our study the incidence of ventricular fibrillation was very low during the taping period and there was no evidence of any increase associated with alteplase. Overall, in the ASSET study the incidence of ventricular fibrillation in hospital was 3·7% in the alteplase group and 4·6% in the placebo treated patients.

It is pertinent to compare the overall pattern of arrhythmias seen in this study with similar studies of streptokinase. After analysis of one minute electrocardiograms taken every hour, Willems and colleagues reported fewer ventricular extrasystoles in the streptokinase treated group, which were attributed to the possibility of smaller infarcts than in placebo group.[16 17] Using intracoronary streptokinase and continuous Holter tape monitoring, Miller and colleagues concluded that both ventricular tachycardia and accelerated idioventricular rhythm were more common with active treatment but bore no relation to the degree of reperfusion achieved.[18] However, in a subset of the GISSI 1 patients, only accelerated idioventricular rhythm was reported to be more common in the treatment group.[19]

Table 5 Frequency of arrhythmias in patients with diagnosis of myocardial infarction

		n	*Mean hours seen*	*Median maximum frequency/h*	*Median total on tape*
VEs	Alteplase	104	17·8*	†	†
	Placebo	108	15·3	—	—
> 30 VEs	Alteplase	58	5·6	†	†
	Placebo	44	7·0	—	—
Fast couplets	Alteplase	80	4·6*	2	4
	Placebo	57	4·3	1	3
Slow couplets	Alteplase	76	5·6*	2	7*
	Placebo	61	4·3	1	3
R on T	Alteplase	7	1·7	2	2
	Placebo	2	1·0	1	1
VTa	Alteplase	68	4·4*	2	4*
	Placebo	54	3·3	1	2·5
VTb	Alteplase	28	1·9	1	1
	Placebo	17	1·5	1	1
VTc	Alteplase	64	4·5	2	6·5
	Placebo	46	3·3	2	3
SVT	Alteplase	34	2·1	1	2
	Placebo	19	1·8	1	2

*Difference between treatments significant at the 5% level.
†Exact number of VEs not counted for many patients but simply recorded as > 30/hr.
See footnote to table 4 for abbreviations



Hourly occurrence of ventricular arrhythmias.

Table 6 Days from admission to death and ventricular tachycardia during first 24 hours

Alteplase (deaths 4)	*Day*	*Placebo (deaths 14)*	*Day*
VT a	2	VT a, VT a/c, VT b/c	1
VT b	4	VT a/c, nil	2
Nil	19	VT a	3
Nil	26	VT a, nil	6
		VT a	7
		Nil	11
		VT a, nil	15
		VT c	18
		Nil	25

VT, ventricular tachycardia.

The incidence, time course, and usually benign nature of the ventricular arrhythmias appearing after thrombolysis with alteplase are very similar to that described by Cercek and colleagues in a study of 45 patients given intravenous streptokinase.[20] Similarly, the pattern described in our placebo group accords with that reported by Campbell and colleagues in a small patient population.[13]

We therefore conclude that, in the context of a hospital coronary care unit, the use of alteplase provokes little more arrhythmias than would otherwise be seen in an individual patient and is no more likely than placebo to precipitate life threatening arrhythmias. Further, if the patient ultimately turns out not to have had an infarct we can be confident that alteplase at least has no arrhythmogenic tendencies. In these respects the findings for alteplase resemble those for streptokinase. If these favourable aspects of thrombolytic treatment obtain in the pre-hospital phase, then another obstacle to even earlier treatment would disappear.[21-23]

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Br Heart J 1991;65:9–13

Holter monitoring of ventricular arrhythmias in a randomised, controlled study of intravenous streptokinase in acute myocardial infarction

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Abstract

The occurrence of ventricular arrhythmias attributed to streptokinase treatment in acute myocardial infarction is not well defined. Holter monitoring was performed for 24 hours in 81 patients with suspected acute myocardial infarction randomised in a ratio of 2:1 to intravenous streptokinase 1·5 × 10^6 IU (n = 55) or placebo infusion (n = 26) 6·7 hours (mean) after the onset of symptoms. No episodes of ventricular fibrillation were recorded. For the whole 24 hour period and during the first three hours after the start of treatment the incidence and frequency of ventricular arrhythmias were similar in the patients randomised to streptokinase and to placebo. But when the results in patients randomised "early" after the onset of symptoms of suspected acute myocardial infarction were analysed separately the frequency of abnormal complexes, pairs, runs, and repetitive arrhythmias seemed to be higher in patients allocated to streptokinase. This may reflect arrhythmias associated with reperfusion.

Streptokinase induced thrombolytic treatment of acute myocardial infarction can reopen occluded vessels,[1–3] improve ventricular function,[4 5] and prolong survival.[6–8] It has, however, been suggested that reperfusion produced by thrombolytic treatment[9–11] may be associated with an increase in the incidence of early ventricular arrhythmias. Conversely, because post-infarction ventricular arrhythmias are more common after larger infarcts,[12] thrombolytic treatment, which seems to reduce infarct size,[4] might be expected to decrease the overall incidence of arrhythmias. There are few controlled studies of the occurrence of ventricular arrhythmias in patients treated with fibrinolytic agents and those treated conventionally.

In the present study, 24 hour Holter monitoring was part of a double blind, placebo controlled randomised trial of intravenous streptokinase in acute myocardial infarction (ISIS-2 pilot[13]) to assess the effects of thrombolytic treatment on ventricular arrhythmias. Arrhythmias occurring in the first few hours after the start of treatment (which might be related to reperfusion) and those occurring later during the first 24 hours (which might be related to infarct size) were assessed separately. Because some studies indicate that reperfusion rates may be inversely related to the time from onset of chest pain to the start of treatment,[2] the influence of this delay on the incidence of ventricular arrhythmias was also investigated.

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Patients and methods

PATIENTS

Between June 1983 and February 1985, 138 patients admitted to the John Radcliffe Hospital Coronary Care Unit were randomised in a placebo controlled study, details of which have been published elsewhere.[13] Patients were eligible if the symptoms of suspected myocardial infarction had started less than 24 hours before and they had no clear indication for or contraindication to streptokinase, heparin, or aspirin (for example history of peptic ulcer, gastrointestinal bleed, stroke, bleeding disorder, recent surgery, resuscitation, or other injury, previous streptokinase treatment, aspirin allergy) and no life threatening condition other than myocardial infarction. A 2 × 2 × 2 factorial randomised study design was used.[13] Two thirds of all patients were allocated randomly to treatment with intravenous streptokinase (1 500 000 IU) and one third to receive a matching placebo,[13] started immediately and infused over about one hour in 20–100 ml of physiological saline. Half of all patients were also allocated randomly to receive enteric coated aspirin (325 mg every 48 hours) and half to receive matching placebo, one tablet each day for 28 days from a calendar pack, started immediately. Similarly, half of all patients were allocated randomly to receive heparin (1000 IU/h for 48 hours, starting 12 hours after the end of the streptokinase/placebo infusion) and half to receive no intravenous heparin, unless it was thought to be clearly indicated. In all other respects, physicians were free to use whatever additional treatment they considered necessary.

RECORDING AND ANALYSIS OF ARRHYTHMIAS

Holter tape recorders were available to start 24 hour electrocardiographic recording immediately before the start of trial treatment in 81 of the 138 Oxford patients (table 1). After the usual skin preparation modified V1 and V5 electrocardiographic leads were recorded on two channel Oxford Medilog II recorders. All patients had more than six hours recording. Two channel qualitative and quantitative electrocardiographic analysis was performed by a computerised non-triggered

Table 1 Clinical characteristics

Variable	*Streptokinase (n=55)*	*Placebo (n=26)*
Pre-randomisation data		
Age (yr)	61·3 (9·7)	57·6 (8·5)
Sex (% male)	78	73
Systolic blood pressure (mm Hg)	130·1 (20·5)	127 (12·8)
Heart rate (beats/min)	73·9 (17·4)	73 (12·6)
Previous myocardial infarction (%)	16	12
Diabetes mellitus (%)	16	0
Time from onset of pain (h)	6·7 (3·2)	6·6 (3·1)
Patients treated within 6 h	4·4 (1·3)	4·4 (1·5)
Patients treated later than 6 h	9·5 (2·8)	9·1 (2·4)
Infarct site		
Anterior-lateral (%)	44	46
Inferior-posterior (%)	56	54
Serum potassium on admission (mmol/l)	3·9 (0·5)	4·1 (0·4)
Post-randomisation data		
Antiarrhythmic agents (in the first 24 hours).		
Lignocaine (%)	4	0
Amiodarone (%)	2	0
Peak enzyme activities during hospital stay.		
AST (IU/l)	432 (279)	363 (270)
LDH (IU/l)	887 (736)	1157 (963)
Holter analysed (h)	23·1 (2·7)	21·7 (4·6)

AST, aspartate aminotransferase, LDH, lactate dehydrogenase.

template system consisting of a Z80A preprocessor and a DEC-LSI master, which had been used in our laboratory for the analysis of complex ventricular arrhythmias.[14] The analysis was made without knowledge of the patient's treatment regimen. The following definitions were used:

(*a*) *Abnormal complexes*—abnormal QRS-shaped complexes with a coupling interval of > 80% of the preceding RR interval.

(*b*) *Ventricular extrasystoles*—abnormal QRS-shaped beats with a coupling interval ⩽80% of the preceding RR interval.

(*c*) *Pairs*—two consecutive abnormal QRS-shaped beats.

(*d*) *Runs*—three or more abnormal QRS-shaped beats with a heart rate < 120/min.

(*e*) *Ventricular tachycardia*—three or more consecutive abnormal QRS-shaped beats with a rate ⩾120 beats/min.

(*f*) *Repetitive arrhythmias*—pairs, runs, and ventricular tachycardia.

When pairs, runs, and ventricular tachycardia were detected by the computer the analysis was automatically stopped and the operator confirmed the pattern. Because of the varying QT interval all ventricular extrasystoles with coupling interval ⩽400 ms were screened carefully to identify and count the R-on-T extrasystoles accurately.

Arrhythmias recorded during the 24 hour study period in patients allocated to a streptokinase infusion were compared with those in patients allocated to a placebo infusion. Arrhythmias occurring in the first three hours after treatment started were also compared with those occurring in the remaining 21 hours. Though the factorial design does in principle allow separate assessment of the effects of aspirin and of heparin, it was not the intent of this arrhythmia study to consider such effects in any detail. Furthermore, because heparin was started 13 hours after the start of Holter monitoring, any differences caused by heparin could only be expected during the later part of the Holter monitoring.

STATISTICAL ANALYSIS

Baseline clinical characteristics were compared by the unpaired Student's t test or χ^2 test as appropriate. We compared the incidence of arrhythmia (percentage of patients with arrhythmias) and their frequency per hour (total number of arrhythmias for each patient divided by the hours of recording) among patients allocated to streptokinase and those allocated to placebo by the χ^2 test and the Wilcoxon rank test, as appropriate. Values were expressed as mean (1 SD) or median and range.

Results

OCCURRENCE OF ARRHYTHMIAS

No episodes of ventricular fibrillation were seen in this small study. Overall there were no significant differences between the streptokinase and the placebo groups in the percentage of patients with ventricular arrhythmias (table 2). Similarly, there were no significant differences betwen the treatment groups in the percentage of patients with arrhythmias within three hours of the start of thrombolytic treatment and the percentage with arrhythmia during the remaining 21 hours. In eight patients, there was a sudden increase in ventricular arrhythmias soon after the start of the infusion. These episodes lasted less than 90 min and were followed by infrequent ventricular arrhythmias during the remaining monitored hours (fig 1). This pattern was more common (but not significantly so) in the streptokinase group (seven patients (13%)) than in placebo group (one patient (4%)).

When patients treated early (that is within six hours) after the onset of symptoms were considered separately, there was no significant difference in the percentage with arrhythmias in the different treatment groups (table 2).

Table 2 Percentage of patients with ventricular arrhythmias recorded on Holter monitoring

	All patients (n=81)		*⩽6 h (n=44)*		*6–24 h*	
	SK (n=55)	*P (n=26)*	*SK (n=30)*	*P (n=14)*	*SK (n=25)*	*P (n=12)*
Abnormal complexes	100	100	100	100	100	100
Extrasystoles	100	100	100	100	100	100
R on Ts	73	88	83	93	60	83
Pairs	82	88	90	93	72	83
Runs	89	77	97	79	80	75
V tach	62	62	63	64	60	58
Repetitive	93	92	97	100	88	83

P, placebo; SK, streptokinase; V tach, ventricular tachycardia.

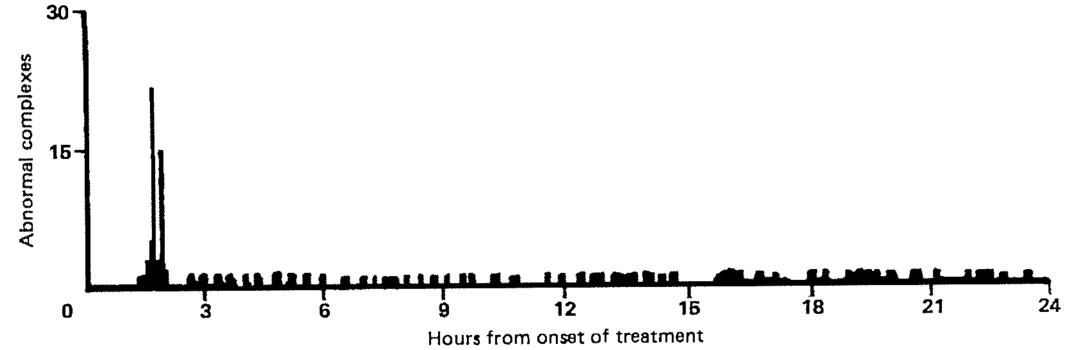

Figure 1 Distribution of abnormal complexes from a patient with sudden increase in arrhythmias shortly after the start of streptokinase infusion.

Table 3 Median frequency (range) per hour of ventricular arrhythmias

	All patients		*≤6 h*		*6–24 h*	
	SK	*P*	*SK*	*P*	*SK*	*P*
Abnormal complexes	3·9 (0·2–390)	2·7 (0·1–76)	7·9 (0·5–390)	2·7† (0·1–76)	2·4 (0·2–11)	2·7 (0·3–69)
Extrasystoles	5·0 (0·3–889)	5·8 (0·5–497)	9·7 (0·6–889)	5·8 (0·5–497)	3·1 (0·3–71)	8·8 (2·1–142)
R on Ts	0·2 (0–41)	0·2 (0–41)	0·2 (0–41)	0·2 (0–26)	0·1 (0–1·3)	0·2 (0–41)
Pairs	0·3 (0–39)	0·2 (0–15)	0·7 (0–39)	0·2‡ (0–15)	0·2 (0–1·3)	0·2 (0–6·4)
Runs	0·3 (0–24)	0·1 (0–12)	0·7 (0–24)	0·2* (0–12)	0·2 (0–1·2)	0·1 (0–2·8)
V tach	0 (0–3·3)	0 (0–0·3)	0·1 (0–3·3)	0 (0–0·3)	0 (0–0·2)	0 (0–0·2)
Repetitive	0·8 (0–60)	0·3 (0–28)	1·7 (0–60)	0·4† (0·1–28)	0·3 (0–2·3)	0·3 (0–9·2)

*2p < 0·02, †2p < 0·01, ‡2p < 0·005.
See footnote to table 2 for abbreviations

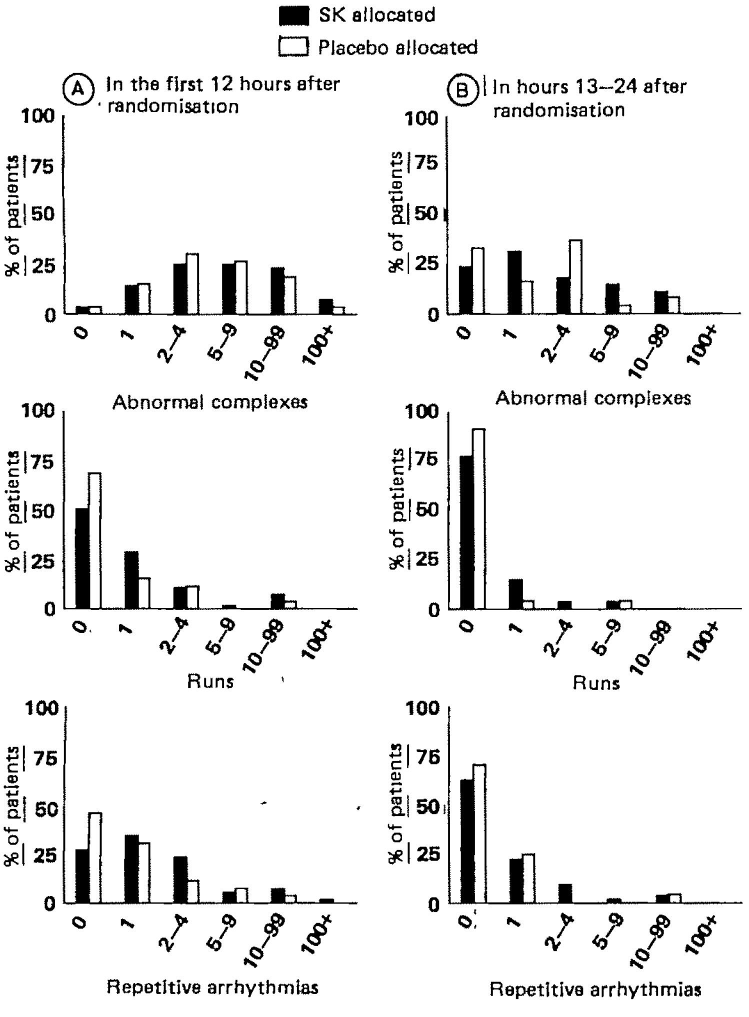

Figure 2 Percentage of patients and mean number of abnormal complexes, runs, and repetitive arrhythmias seen during the first 12 hours and 13–24 hours from randomisation SK, streptokinase.

HOURLY FREQUENCY OF ARRHYTHMIAS

Overall there were no significant differences between the streptokinase and the placebo groups in the average hourly frequency of ventricular arrhythmias (table 3). The hourly frequency of arrhythmias recorded within three hours of the onset of treatment and during the remaining 21 hours of recording was similar in the treatment and placebo groups. But for patients treated within six hours of the onset of pain there were significant differences between the treatment groups in the frequency of abnormal complexes, of pairs, of runs, and of repetitive arrhythmias (table 3). This seemed to be largely the result of an increase in such arrhythmias during the first 12 hours after treatment (figs 2–4) and was not apparent among patients treated 6–24 hours after the onset of pain (table 3).

Discussion

There is little detailed information from Holter monitoring on the effects of fibrinolytic treatment on arrhythmias. To our knowledge, only two previous studies have attempted quantitative analysis of post-thrombolysis arrhythmias by continuous electrocardiographic monitoring. Willems *et al* used a low initial intravenous streptokinase dose regimen (250 000 IU initially, followed by 100 000 IU/hour for 24 hours) and they found no overall difference in the number of extrasystoles.[15] Differences in baseline arrhythmias and in the use of antiarrhythmic agents, however, were considered by these workers to have limited the value of their study. More recently, in a study of 750 000 or 1 500 000 IU of intravenous

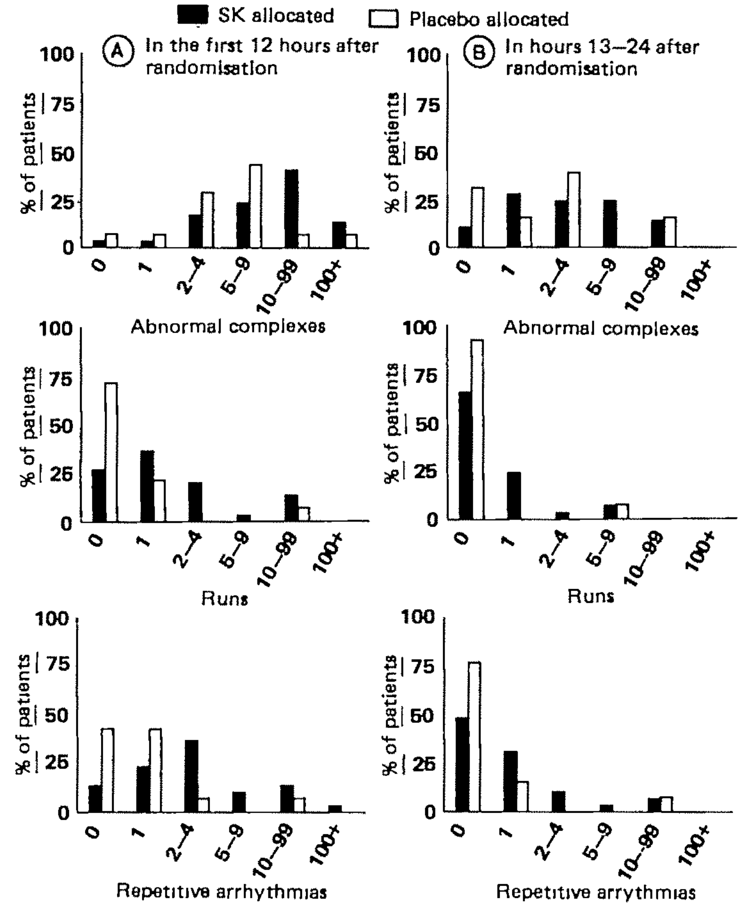

Figure 3 Percentage of patients treated within six hours from onset of symptoms and mean number of abnormal complexes, runs, and repetitive arrhythmias seen during the first 12 hours and 13–24 hours from randomisation. SK, streptokinase.

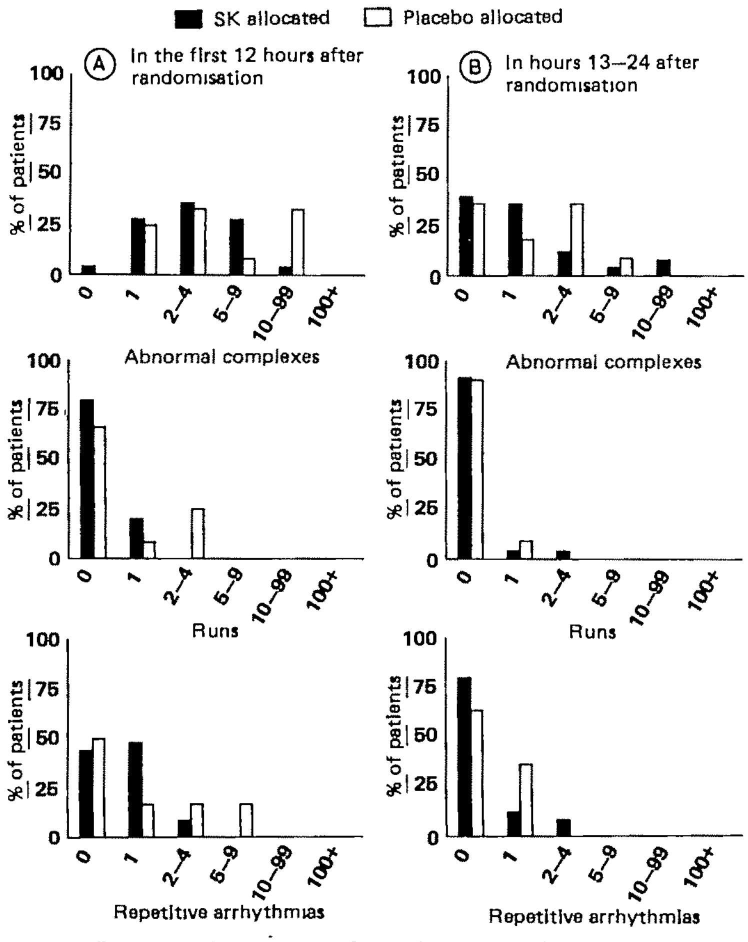

Figure 4 Percentage of patients treated more than six hours from onset of symptoms and mean number of abnormal complexes, runs, and repetitive arrhythmias seen during the first 12 hours and 13–24 hours from randomisation. SK, streptokinase.

streptokinase given over about 2·5 hours), Cercek *et al* reported on the percentage of patients with arrhythmias attributed to reperfusion defined by non-invasive indices.[16] There was, however, no control group in this study with which to compare the patients given fibrinolytic treatment.

In the large GISSI trial conventional (that is non-Holter) electrocardiographic monitoring detected early arrhythmia in only 1·2% of the patients allocated to streptokinase treatment but in this trial the frequency of early arrhythmias was not recorded in the open-control patients.[7] In a subgroup of 433 patients participating in GISSI, arrhythmic events were recorded by computerised coronary care or Holter monitoring during the first two hours after randomisation. No clear differences were demonstrated between the patients allocated to the streptokinase and control groups.[17]

Ventricular fibrillation was not seen in any patient in the present Holter study, but this is not surprising given its small size. In the large ISIS-2 trial, the observed incidence of ventricular fibrillation during the first 24 hours after the start of treatment was similar in the patients allocated to streptokinase and placebo (2·8% *v* 2·8%, unpublished data), while ventricular fibrillation during hospital admission was somewhat less common in patients allocated to streptokinase (4·3% *v* 4·9%). A similar, non-significantly lower incidence of ventricular fibrillation in hospital was also seen in the GISSI and recent trials of other fibrinolytic agents.[18 19]

The intention of the present Holter study was to assess the effects of streptokinase on arrhythmias in a randomised controlled study. Streptokinase did not seem to increase the overall percentage of patients with arrhythmia or the overall frequency of arrhythmias among the patients entered in the study, though there was a suggestion that streptokinase might be associated with an increased frequency of abnormal complexes, of runs, and of repetitive arrhythmias among patients treated early after the onset of pain. Because angiographic data were not available for patients in this study, this apparent excess of arrhythmias cannot be attributed definitely to myocardial reperfusion, though this seems to be a plausible hypothesis worthy of further study.

In this study intravenous streptokinase treatment seemed to have a low arrhythmogenic potential (and, indeed, larger studies suggest that serious arrhythmias may be less common with fibrinolytic treatment). Consequently, there may be little need for treatment with prophylactic antiarrhythmic agents in patients given fibrinolytic treatment, particularly in view of the lack of evidence for any benefits of these agents[20] in the treatment of suspected acute myocardial infarction when fibrinolytic treatment is not used.

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We thank Dr Sarah Parish and Mr Paul Appleby for assistance with computer programming

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Prognostic value of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method

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Abstract

The relation between heart rate variability, measured from standard 24 hour electrocardiogram recordings in patients convalescent after a myocardial infarction, and the occurrence of sudden death and spontaneous, symptomatic, sustained ventricular tachycardia were assessed in a consecutive series of 177 patients admitted with acute myocardial infarction and surviving to 7 days. In addition to the analysis of heart rate variability, the occurrence of non-sustained arrhythmias on 24 hour electrocardiographic monitoring, and the results of clinical assessment, signal averaged electrocardiography and ejection fraction were analysed and were related to outcome. During a median of 16 months of follow up (range 10–30 months) there were 17 end point events (11 (6·2%) sudden deaths) and six (3·4%) episodes of sustained ventricular tachycardia. An index of the width of the frequency distribution curve for the duration of individual RR intervals was used to measure heart rate variability. This mean (SD) index was significantly smaller in those with end point events (16·8 (8·0)) than in those without events (29·0 (11·2)). The relative risk of the occurrence of an end point event in those with a heart rate variability index <25 was 7·0. Multivariate analysis showed that of all the variables examined a reduced heart rate variability index was the single most powerful predictor of end point events.

Measurement of heart rate variability by this simple, automated, operator-independent method provided useful information on the arrhythmic propensity in patients convalescent after myocardial infarction.

Reduced heart rate variability, expressed as the standard deviation of RR intervals recorded on a 24 hour electrocardiogram in patients convalescent after myocardial infarction, was related to mortality during follow up.[1] It is thought that decreased heart rate variability results from a relative decrease in parasympathetic activity in relation to sympathetic activity, and that this facilitates arrhythmogenesis.[2]

The standard deviation method for measuring heart rate variability can be laborious, because noise and artefact (from which no clinical quality long term electrocardiogram recording is completely free) can considerably influence the results. Visual checking and correction are therefore required.[1]

We devised a simple, arithmetic method to produce an index of heart rate variability from clinical quality long term electrocardiogram recordings without the need for rigorous checking or correction, so that the analysis can be carried out rapidly and independently of operator skill in the clinical setting.[3] We have assessed the prognostic value of analysis of heart rate variability by this method, in relation to other prognostic variables including clinical assessment, signal averaged electrocardiography, measurement of ejection fraction, and non-sustained ventricular arrhythmias on long term electrocardiographic recordings, in a consecutive series of convalescent patients after infarction.

Patients and methods

PATIENTS

All patients aged ≤70 admitted to the hospital between 1 May 1986 and 1 June 1988 as general medical emergencies having sustained an acute myocardial infarction within the previous 24 hours were seen within 48 hours of admission and were considered for inclusion in the study, which was approved by the regional ethics committee. Acute myocardial infarction was diagnosed when two or more of the following features were present: (*a*) chest pain suggestive of myocardial ischaemia persisting for at least 20 minutes and unrelieved by glyceryl trinitrate; (*b*) a sequential rise and fall in the plasma concentrations of aspartate transaminase, 2-hydroxybutyrate dehydrogenase, and/or creatine kinase with a peak concentration at least twice the upper limit for our laboratory; and (*c*) the development of new abnormal Q waves or persistent ST/T changes suggestive of non-Q wave myocardial infarction. Patients were ineligible if they had non-cardiac disease likely to influence mortality, important non-ischaemic cardiac disease, a history of previous cardiac surgery or permanent pacemaker insertion, and if they refused or were unable to attend for follow up. Because this was a long term prognostic study, we also excluded patients who died or had cardiac surgery within 7 days of the onset of myocardial infarction—the usual time of hospital discharge. Patients transferred from other hospitals to the regional cardiothoracic unit with complications of acute myocardial infarction were not included, so that the population studied would be representative of patients admitted to a general hospital and surviving to discharge after myocardial infarction. Those with previous infarction were included, as were those with Q and non-Q wave infarction.

CLINICAL ASSESSMENT

Infarct site (anterior or inferior/posterior) and type (Q or non-Q) was determined from all electrocardiograms recorded during admission including one at discharge. A Q wave was defined as an initial negative deflection of either or both (*a*) 40 ms duration and (*b*) at least 25% of the amplitude of the succeeding R wave. The Killip class on admission was noted and the patients were reviewed daily by one of us (TRC) to document the occurrence of in-hospital complications. The important in-hospital complications were cardiogenic shock (defined as a systolic blood pressure <90 mm Hg with evidence of inadequate cardiac output), radiographic pulmonary oedema, persistent tachycardia (heart rate >100 beats/minute on the third or subsequent day), post-infarction angina or reinfarction, and blood urea >8·4 mmol/l).

LONG TERM ELECTROCARDIOGRAPHIC MONITORING AND ANALYSIS OF RR INTERVAL

Twenty four hour electrocardiographic monitoring was carried out by conventional techniques more than 5 days after infarction (median 7 days). In no case was the recording made after an end point had occurred. A Tracker recorder (Reynolds Medical, Hertford) was used. The patients were encouraged to continue their daily activities while the recording was made, and their medication at the time of recording was noted.

Tapes were analysed for the incidence of arrhythmias and the variability of the RR interval. We used a standard operator-computer interactive method with a commercially available device for tape analysis (Pathfinder III, Mark II, Reynolds) to measure the frequency of extrasystoles and the occurrence of couplets, non-sustained ventricular tachycardia, and multiform ventricular extrasystoles. The analysis system identified the different shapes of the aberrant beats; the triggering level for this identification can be adjusted by the operator. In each patient we did an initial standard check to ensure that normal and extrasystolic complexes were triggering the equipment correctly. A frequency of >10 extrasystoles/hour was regarded as abnormal[4]; no patient was given antiarrhythmic treatment on the basis of the long term electrocardiogram recording.

To measure the variability of the RR interval we digitised the tapes and transferred the digital information via a serial link to a personal computer (IBM PC-AT). Each beat was tagged as normal or aberrant according to its recognition by the algorithm for tape analysis. A frequency distribution for all of the normal-normal RR intervals was then generated, and the mean RR interval duration, the modal RR interval frequency, the standard deviation of all the normal-normal RR intervals, and the total number of recognised normal complexes were recorded (fig 1). Aberrant-normal and normal-aberrant beat intervals were excluded from analysis. Only normal-normal beat intervals were analysed.

The development of the most meaningful method for quantifying heart rate variability from such data was described elsewhere.[3] We found that the use of the standard deviation of RR intervals was not the most meaningful method, because, as can be seen from fig 1, artefact can heavily weight the result. One approach to this is to check and eliminate the artefactual intervals visually. The alternative approach, which we have adopted, is to devise an arithmetic method of expressing heart rate

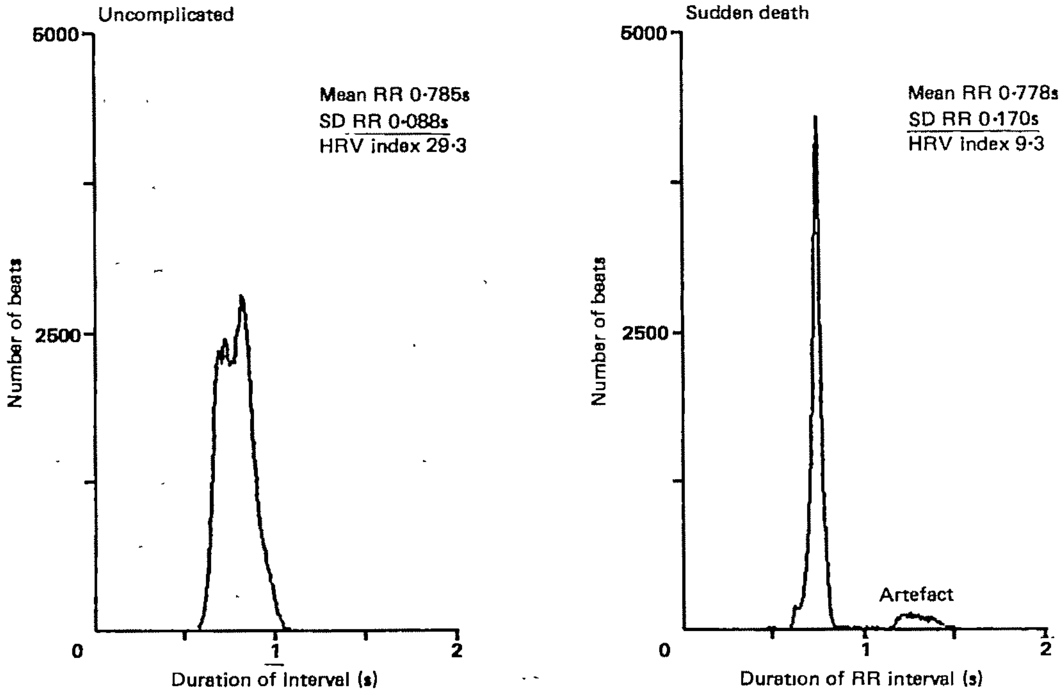

Figure 1 Frequency distribution curves for a patient who died suddenly during follow up and one with an uncomplicated course. Though the curve for the patient who died was narrower, quantification of heart rate variability by the standard deviation (SD RR) is misleading because of the presence of artefact. The heart rate variability (HRV) index, however, faithfully represents the visual impression of a lower variability in the patient who died.

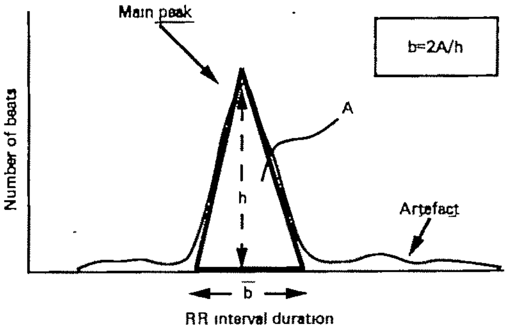

Figure 2 Triangular method for analysis of heart rate variability. The main peak of the RR interval frequency distribution diagram is approximated to a triangle. Heart rate variability is quantified from the length of the base of this triangle, calculated according to simple geometrical rules.

variability that is resistant to the low level of artefact found in clinical quality 24 hour tape recordings.

Of all the arithmetic methods tested[3] the best for discrimination between post-infarction recordings from patients with and without arrhythmic events was the method shown in fig 2. If the main peak on the frequency distribution diagram for computer-recognised RR intervals is regarded as a triangle, its baseline width (b) (which expresses the amount of RR interval variability) can, according to simple geometrical rules, be calculated from the triangle's height (h) and area (A). The "height" is equal to the most frequently observed duration of RR interval (the modal frequency) and the "area" is (since the frequency of artefactual intervals is small compared with the frequency of the non-artefactual ones) approximately equal to the total number of computer recognised RR intervals. This "triangular index" is thus derived from a trivial calculation:

Triangular index = total number of intervals/modal RR interval frequency.

The dimensions of the index are related to time, but we think that it is clearer to leave the index without units.

The triangular index tends to exaggerate the variability when the distribution of RR intervals is bimodal or polymodal, but since in such cases the variability is necessarily greater than where the frequency distribution consists of a single, narrow peak, which tends to be the case in the complicated cases (fig 1) this effect tends if anything to increase the ability of the method to distinguish the high risk cases.

HIGH GAIN, SIGNAL AVERAGED ELECTROCARDIOGRAM

Signal averaged electrocardiography was carried out with a commercially available high resolution electrocardiograph (Arrhythmia Research Technology, Model 1200 EPX) at a median of five days after infarction. The principles and operation of this device were reported elsewhere.[5] The high-pass filter was set at 25 Hz and 100–200 beats were averaged to achieve a final noise level of $< 0{\cdot}8$ μV. We defined the presence of late potentials by Simson's criteria[5]: a prolonged filtered QRS alone was not regarded as a positive criterion if the QRS duration measured from the standard electrocardiogram was > 120 ms. In all cases, the recording was performed at the bedside and completed within five minutes. No patient was given antiarrhythmic treatment on the basis of the signal averaged electrocardiogram results.

EJECTION FRACTION MEASUREMENT

Where possible left ventricular function was assessed from global left ventricular ejection fraction in all patients within the first month after infarction. If angiography was performed, the left ventricular end systolic and end diastolic volumes were measured by planimetry from the right anterior oblique projection and the ejection fraction was calculated by the Dodge formula. If angiography was not performed the ejection fraction was measured by standard radionuclide techniques.

FOLLOW UP

All patients were followed up at regular intervals in the outpatient clinic. Careful inquiries were made of the relatives and general practitioners of non-attenders to determine whether they had died and, if so, the mode of death. The primary end point was the occurrence of an arrhythmic event outside the context of reinfarction (sudden death or spontaneous, symptomatic, sustained ventricular tachycardia more than 48 hours after the onset of infarction).

Sudden death was defined as death within an hour of the onset of symptoms. Ischaemic events included reinfarction (defined as for the initial infarction (see above) in patients in hospital) or the occurrence of persistent uncharacteristic ischaemic type pain in those dying out of hospital.

The end points were chosen because they seemed most appropriate for a study seeking to predict ventricular tachycardia, as distinct from mortality from all causes, especially reinfarction, which tests such as the signal averaged electrocardiogram and heart rate variability analysis would not be expected to predict.

Because the population was a geographically stable one and relatively small, through personal contact we were able to discover the outcome in all who did not attend an outpatient appointment.

STATISTICAL ANALYSIS

We compared groups of continuous variables by the two group two tailed t test and discrete variables by the χ^2 test with Yates's correction where appropriate.

We used the following definitions: ***sensitivity***, percentage of patients with an event who had a positive test result—that is, true positive/true positive + false negative; ***specificity***, percentage without an event with a negative result—that is, true negative/true negative + false positive; ***positive predictive accuracy***, percentage of patients with a positive test result who suffered an event—that is true positive/true positive + false positive; ***negative predictive accuracy***, percentage with a negative test without an event—that is, true negative/true negative + false positive; ***efficiency***, percentage with correct test result—that is, true positive + true negative/total; ***relative risk***, risk of suffering an event in those with a positive test compared with those with a negative test—that is, positive predictive accuracy/(false positive/total negative).

Multivariate analysis was carried out using

Table 1 Clinical characteristics of included and excluded patients

	Tested	*Not tested*	*p*
Number	177	53	—
Age (yr)	56 (9)	57 (9)	NS
Sex (% female)	19	19	NS
Infarct site (% anterior)	51	47	NS
Q wave (%)	66	63	NS
Previous AMI (%)	11	22	<0·04
Killip class > II (%)	5	15	<0·02
IHC (%)	31	43	NS
Ejection fraction (%) (SD)	54 (14)	50 (21)	NS
Death rate (%)	6	21	<0·002

AMI, acute myocardial infarction, IHC, occurrence of in-hospital complications.

Table 2 Results (mean (SD)) of 24 hour electrocardiographic monitoring in patients with events and without

	Sudden death and VT	*No events*	*p*
Mean RR interval (s)	0·71 (0·09)	0·87 (0·15)	<0·0001
Standard deviation RR	0·12 (0·09)	0·12 (0·05)	NS
HRV index	16·8 (8·0)	29 (11·2)	<0·0001
Extrasystolic frequency (/ h)	13·2 (22·5)	7·3 (25·7)	NS

HRV index, heart rate variability index; standard deviation RR, heart rate variability by the standard deviation method, VT, ventricular tachycardia

the Cox proportional hazards model and the PHGLM procedure in the SASS mainframe program. Throughout the study probability values of <0·05 were regarded as statistically significant.

Results

PATIENTS

During the period of the study 230 patients were admitted to the hospital with myocardial infarction and were eligible for entry to the study according to the exclusions listed in the methods section. Four were excluded because of life threatening non-cardiac disease; two because of important non-ischaemic cardiac disease; eight because of prior cardiac surgery; two because they had permanent pacemakers, and two who refused or were unable to attend follow up.

Of the remaining patients, the tapes of six were not suitable for analysis of heart rate variability because of atrial fibrillation; in 11 technical problems prevented analysis (three completely blank, five with barely discernible R waves, and three destroyed by the tape transport mechanism), and in 36 there was no tape available. There were thus 177 patients whose tapes underwent analysis. In no case did we reject a tape of a quality acceptable for clinical arrhythmia analysis for heart rate variability analysis.

There was no significant difference (table 1) between eligible patients who did and did not undergo heart rate variability analysis in terms of age, sex, infarct site or type, the occurrence of important in-hospital complications, or ejection fraction. There was a slightly higher incidence of previous infarction, Killip class > II, and death in those not tested: this was because several patients in whom the initial recording was not done or was not satisfactory could not undergo a repeat recording because they died soon after discharge. The clinical characteristics of the study population (table 1) show that it was comparable with other reported populations of patients surviving to discharge after acute myocardial infarction.

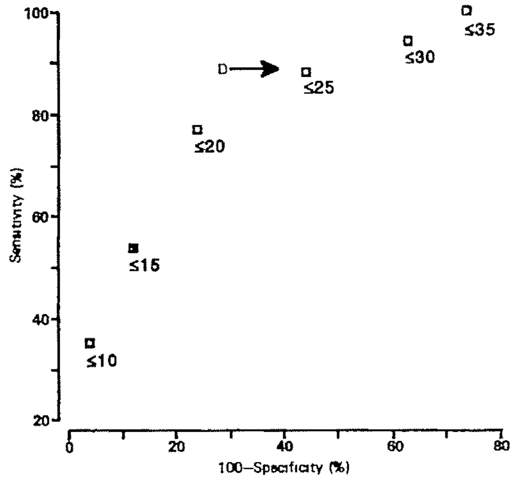

Figure 3 Receiver-operator characteristic curve (ROC curve) for heart rate variability index. The division between normal and abnormal values is indicated (D)

FOLLOW UP

Follow up of the study group was complete, with none lost, and continued for a median of 16 months (range 10–30 months). During this time, 17 patients (9·6%) experienced end point events—11 sudden deaths (6·2%) and six (3·4%) spontaneous symptomatic sustained ventricular tachycardias. There were two other deaths, one in a patient admitted with reinfarction who died of progressive cardiogenic shock culminating in electromechanical dissociation and one with atrial fibrillation who died in pulmonary oedema.

LONG TERM ELECTROCARDIOGRAM RECORDINGS

Table 2 shows the results of the long term electrocardiogram analysis, both for frequency of extrasystoles and heart rate variability. The mean RR interval was shorter (heart rate higher) in those with events than in those without events, and the heart rate variability

Table 3 Value of 24 hour tape variables in predicting sudden death and ventricular tachycardia

	Sens (%)	*Spec (%)*	*PPA (%)*	*NPA (%)*	*Eff (%)*	*Relative risk*
HRV index <25	87	56	15	98	58	7·0
Standard deviation RR <50 ms	67	63	14	95	63	3·1
Frequency of extrasystoles >10/h	40	85	20	94	81	3·3
Multiform extrasystoles	59	66	15	94	65	2·5
Non-sustained VT	29	91	21	92	85	3·5

HRV index, heart rate variability index, Eff, efficiency, NPA, negative predictive accuracy; PPA, positive predictive accuracy; Sens, sensitivity, Spec, specificity; standard deviation RR, heart rate variability by the standard deviation method; VT, ventricular tachycardia.

Table 4 Relation between heart rate variability index and nature of end point event

	n	*Events*	*No events*	*p*
Arrhythmic events	17	16·8 (8 0)	29 0 (11 2)	0 0001
Ischaemic events	13	29·7 (15 4)	27 7 (11 2)	NS

	Sens	*Spec*	*PPA*	*NPA*	*Eff*	*Relative risk*
Arrhythmic events	87	56	15	98	58	7 0
Ischaemic events	38	51	6	91	50	0 7

See footnote to table 3 for abbreviations.

index was lower in those with events. There was no significant difference between the two groups, however, in terms of the mean extrasystolic frequency or the standard deviation of RR interval durations. There was no correlation between the results of analysis of heart rate variability and mortality from all causes.

The mean number of recognised normal-normal RR intervals analysed was 98 581; in no case were fewer than 75 000 intervals analysed. No patient had an aberrant beat count of > 500 in 24 hours, and so it is clear that nearly all recognised intervals were normal-normal intervals.

Table 3 shows the results of dichotomising the 24 hour tape data into positive and negative test results. The point chosen for dichotomy was at the previously suggested level of 10 extrasystoles per hour[4] and at 50 ms for the standard deviation of RR intervals.[1] For the heart rate variability index we selected the point of optimum trade-off between sensitivity and specificity (fig 3). The optimum dichotomy points for extrasystolic frequency and standard deviation of RR intervals from our data resembled previously published values.

It is clear that, while there is an increased risk of end point events with the traditional 24 hour tape variables, namely a higher frequency of extrasystoles, multiform extrasystoles, the occurrence of non-sustained ventricular tachycardia, and a reduced standard deviation for RR intervals, the heart rate variability index is far more powerful as a predictor of primary end point events with a relative risk of event occurrence of 7·0 in those with a heart rate variability index < 25.

Table 4 shows the prediction of arrhythmic and ischaemic events by the heart rate variability index. It seems that a reduced heart rate variability index tends to be associated, as would be expected, primarily with arrhythmic rather than ischaemic events.

OTHER PROGNOSTIC VARIABLES

Table 5 shows the results of the other prognostic tests in relation to the occurrence of end points. In 11 patients the result of the signal averaged electrocardiogram was not available, either because of bundle branch block or technical problems and in 36 the ejection fraction data were not available for administrative reasons. Table 5 shows that, unlike the other prognostic variables, reduced heart rate variability is powerfully associated with the occurrence of end point events.

MULTIVARIATE ANALYSIS

The results of multivariate analysis showed that though several of the known prognostic variables tested were individually associated with the occurrence of end point events, the single most powerful prognostic variable was the presence of a reduced heart rate variability index (β coefficient $-0{\cdot}159$; adjusted χ^2 10·2, $p < 0{\cdot}0014$). A reduced heart rate variability index of < 25 provided independent prognostic information above that provided by age and mean heart rate, and the use or avoidance of β blockers.

Discussion

This study had two aims: firstly, to apply a novel, simplified, wholly automated method for the analysis of the variability of heart rate over a 24 hour period[3] to a large population of patients convalescent after myocardial infarction; and, secondly, to relate the prognostic significance of reduced heart rate variability to other, recognised prognostic variables after infarction.

Our results showed that the heart rate variability index we used gave clinically meaningful information. The relative risk of sudden death or the development of symptomatic, sustained ventricular tachycardia during follow up was seven times greater in those with an index of < 25 than in those with an index of ⩾25 (table 3). This index was a much better predictor than the conventional 24 hour tape variable (an extrasystolic frequency of > 10 per hour) both in terms of relative risk and sensitivity. As expected, however, the mean heart rate, presumably a reflection of infarct size, was also different in those with events and without. Multivariate analysis, however, showed that reduced heart rate variability did provide prognostic information independent of mean heart rate.

The other prognostic variables examined also provided useful information: the occurrence of late potentials, a reduced ejection fraction, and clinical evidence of major infarction were all associated with a relative risk of 2–4 of the occurrence of end point events

Table 5 Comparison of value of heart rate variability index with other prognostic tests for the prediction of sudden death and ventricular tachycardia

Test	*Sens*	*Spec*	*PPA*	*NPA*	*Eff*	*Relative risk*
Heart rate variability index	87	56	15	98	58	7 0
Presence of late potentials	50	80	19	95	78	3·5
Admission Killip class II	18	96	33	92	89	4 0
In-hospital complications	65	74	21	95	73	4 3
Ejection fraction 40%	22	89	10	96	86	2 2

See footnote to table 3 for abbreviations.

(table 5). Each individual test, however, seemed to be less powerful than reduced heart rate variability in predicting the occurrence of sudden death and spontaneous, sustained ventricular tachycardia.

Only a small number of end points occurred in our relatively small population, and so it is not possible to extrapolate the results of this study to other populations with any confidence. Calculated confidence intervals are 74 to 100% for sensitivity, 48 to 64% for specificity, and 0 to 55% for predictive accuracy. However, our results are in accord with the other large scale study of heart rate variability analysis in post-infarction patients.[1]

Our study was retrospective in the sense that the division between a normal and an abnormal index of heart rate variability was selected to give the best discrimination between patients with and patients without arrhythmic events. The prognostic value of the index was thus optimised, and a proper comparison with the other prognostic variables must await further prognostic studies. Because the technique we describe is simple and rapid to perform, such studies are entirely feasible. Also, in the multivariate analysis, heart rate variability was treated as a continuous variable, and so the results were not biased by a favourable division into normal and abnormal.

Our result depended, of course, on the beat recognition method used by the long term electrocardiogram analysis system. Different systems should be studied too.

In this study we did not further investigate the mechanism of the relation between reduced heart rate variability and the occurrence of arrhythmic events. It seems that reduced heart rate variability reflects a disturbance of sympathovagal interaction towards a decrease in parasympathetic activity.[6] Such an imbalance is thought to facilitate the emergence of ventricular tachycardia.[7] Increased sympathetic activity is of course related to impaired left ventricular function, but multivariate analysis showed that in this population a reduction in heart rate variability did provide prognostic information above that obtainable from recognised indices of left ventricular impairment, including the ejection fraction. In other words, not all of those with large infarcts were at increased risk of arrhythmic events; the presence of reduced heart rate variability helped to focus more accurately upon those who were.

Efficient risk stratification after myocardial infarction is desirable, to reassure the low risk group, to spare this group further investigation and treatment, and to focus attention upon the high risk patients, on whom novel treatments can be tested effectively. It seems that analysis of heart rate variability can add to the accuracy of non-invasive prognostic stratification after acute infarction; the method of analysis we have described has the advantage of being computationally simple, rapid, repeatable, and operator independent.

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Direct measurement of skeletal muscle fatigue in patients with chronic heart failure

Nigel P Buller, David Jones, Philip A Poole-Wilson

Abstract

Skeletal muscle function was measured as force production and fatigue in both the quadriceps (a large locomotive muscle) and adductor pollicis (a small intrinsic hand muscle) in five healthy volunteers, five patients with mild chronic heart failure, and five patients with severe chronic heart failure. The quadriceps of patients with chronic heart failure had a reduced muscle cross sectional area, a reduced maximum isometric force production, and an increased tendency to fatigue. Isometric force production and fatigue of the adductor pollicis, however, were not significantly different between the three groups under control conditions. But during circulatory occlusion fatigue in the adductor pollicis increased more in the patients with severe chronic heart failure. These differing findings in quadriceps and adductor pollicis suggest that skeletal muscle atrophy and reduced isometric force production are not a necessary consequence of chronic heart failure per se, because they were only present in the large locomotive muscle. The normal values for muscle fatigue observed in adductor pollicis in patients with chronic heart failure imply that skeletal muscle blood flow must increase normally during muscle activation when only a small muscle mass is used. These results are not compatible with the concept of a generalised impairment of normal vasodilatation within active skeletal muscle. In contrast, activation of a large muscle, such as quadriceps, results in the rapid onset of fatigue in patients with severe chronic heart failure. This fatigue may be related to the inability of the cardiovascular system to provide the required blood flow for the activation of a large muscle mass. The finding of a relatively greater increase in fatigue of adductor pollicis during circulatory occlusion in patients with severe chronic heart failure supports the hypothesis of an intrinsic abnormality of skeletal muscle in these patients.

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Exertional fatigue is a major symptom of patients with chronic heart failure.[1] The mechanisms underlying this symptom are complex, but it has been established that reduced skeletal muscle blood flow on exercise is an important factor.[2] The relative contributions to the reduced skeletal muscle blood flow of a reduced cardiac output and impaired vasodilatation within the skeletal muscle vascular bed are still unresolved.[3-5] There is also evidence from studies with magnetic resonance spectroscopy of an intrinsic intracellular abnormality of skeletal muscle biochemistry in chronic heart failure.[6 7] A study of exercise involving a small muscle mass in patients with chronic heart failure showed abnormal muscle biochemistry despite normal skeletal muscle blood flow.[7]

We report on the direct measurement of skeletal muscle function in both the quadriceps (a large locomotive muscle) and the adductor pollicis (a small intrinsic hand muscle). The purpose of this study was to answer three questions. First, does the direct measurement of skeletal muscle fatigue correlate with the severity of chronic heart failure? Second, is fatigue dependent on the size of the muscle mass activated? Third, are factors other than skeletal muscle blood flow important in the genesis of fatigue in patients with chronic heart failure?

Patients and methods

The protocol was approved by the hospital ethics committee and all subjects gave informed consent.

Patients

We studied 15 right handed men (table): five healthy volunteers, five patients with mild or moderate chronic heart failure ($\dot{V}O_2$ max 15–25 ml/min/kg), and five patients with severe chronic heart failure ($\dot{V}O_2$ max <15 ml/min/kg). We excluded patients with diabetes, thyroid dysfunction, neurological disease, arthritis, or orthopaedic abnormality. The cause of chronic heart failure was ischaemic heart disease. The five patients with mild heart failure were all in sinus rhythm. None was taking digoxin and three were taking an angiotensin converting enzyme inhibitor. The mean dose of frusemide was 56 mg/day. Of the five patients with severe heart failure one was in atrial fibrillation, two were taking digoxin, and all were taking an angiotensin converting enzyme inhibitor. The mean dose of frusemide was 112 mg/day. All patients were ambulant and considered to be receiving optimal oral medication at the time of the study.

Table *Results in adductor pollicis and quadriceps*

Group	Age (years)	$\dot{V}o_2$ max (ml/min/kg)	Adductor pollicis: Maximum force (N)	Control fatigue (%)	Ischaemic fatigue (%)	Ratio	Quadriceps: MVC (N)	Fatigue (%)
Healthy volunteers.								
1	30	—	37	54	32	59	480	100
2	42	—	60	52	28	54	510	98
3	36	—	26	43	26	60	495	98
4	32	—	89	26	18	69	450	102
5	60	—	89	24	15	63	400	78
Mild heart failure								
6	65	15	40	50	26	52	356	80
7	62	18	42	33	23	70	332	88
8	63	23	63	31	16	52	416	72
9	49	20	40	28	21	75	445	92
10	66	16	56	27	13	48	380	86
Severe heart failure								
11	56	11	36	92	35	38	300	57
12	41	14	58	61	18	30	335	70
13	57	10	67	51	21	41	280	51
14	42	9	44	44	10	23	360	60
15	43	12	71	33	11	33	340	59

MVC = maximum voluntary contraction.

QUADRICEPS PROTOCOL

Skeletal muscle function was measured in the late morning, before lunch. The subject was seated within a rigid framework with the lower limbs hanging freely (fig 1). The right ankle was attached by an inelastic strap to a force transducer; the strap was adjusted so that it was perpendicular to the ankle. The subject wore a seat belt around the waist to prevent forward movement during quadriceps contractions. Two large saline pad electrodes were placed on the anterior aspect of the right thigh for direct transcutaneous stimulation of quadriceps muscle fibres. These electrodes were held in position by a crepe bandage. After amplification the output from the force transducer was displayed on an oscilloscope to provide visual feedback to the subject and simultaneously recorded on a UV chart recorder for subsequent analysis. The stimulating electrodes were connected to a Devices stimulator which was set to deliver a pulse duration of 1 ms at a frequency of 1 Hz. After an intial period during which the subject was familiarised with the visual feedback of force production, the output voltage of the stimulator was slowly increased to produce a muscle twitch of at least 20 N. The subject was then instructed to pull as hard as possible on the ankle strap for about three seconds. The voluntary contraction was accepted as maximal only if the superimposed 1 Hz muscle twitch was abolished during the plateau of force production[8] (fig 2). After maximum activation the subject rested for one minute, and then performed two further maximal contractions. The mean of the three maximum voluntary contractions was obtained by direct measurement from the UV chart recorder. The subject then rested for five minutes without muscle stimulation.

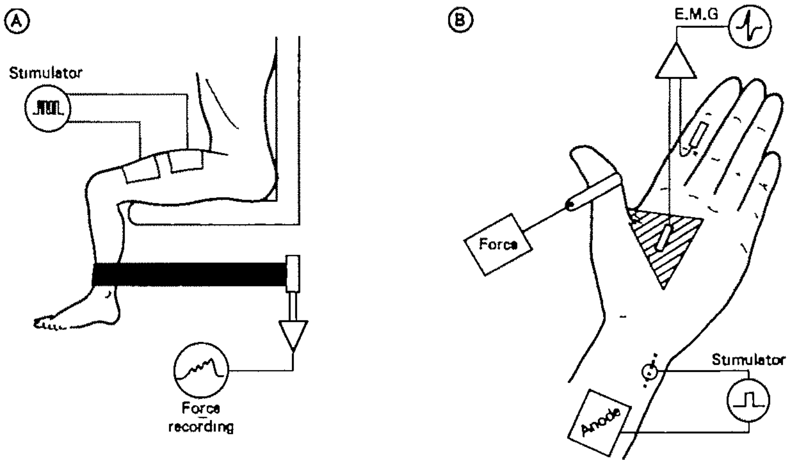

Figure 1 *Experimental procedures used to measure mechanical function of the quadriceps (A) and adductor pollicis (B) (see text for details). EMG, electromyogram.*

For the quadriceps fatigue protocol we set a visual target equal to 30% of the individual's measured maximum voluntary contraction. The subject then performed one second contractions followed by one second relaxations for 40 seconds. A metronome was used to facilitate coordination. This sequence was repeated each minute for 20 minutes. Maximum voluntary contraction was measured again at the end of the fatigue protocol. Fatigue was measured as the maximal voluntary force production at the end of the protocol expressed as a percentage of the initial maximal voluntary contraction.

At the end of the fatigue protocol the five patients with severe chronic heart failure had the cross sectional area of the quadriceps measured on computed tomography scans taken at mid-femur level by the method of Jones *et al.*[9] In addition, a needle biopsy from the quadriceps was obtained from five patients (three with severe chronic heart failure and two with mild chronic heart failure) by the suction technique described by Edwards *et al.*[10] Some of the muscle specimen was taken for histology and histochemical examination and the remainder was used to measure mitochondrial enzyme activities.

ADDUCTOR POLLICIS PROTOCOL

The subject sat at a bench and the left hand was immobilised in a padded Perspex cast. A

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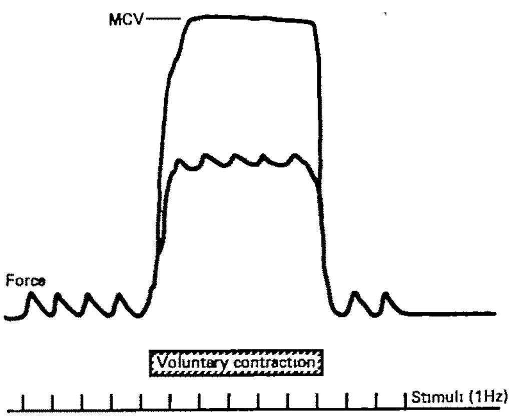
Figure 2 Twitch interpolation technique used to ensure full quadriceps activation during measurement of maximum voluntary contraction.



stirrup was placed over the thumb at the level of the interphalangeal joint, and connected by means of an inelastic link to a force transducer (fig 1). Surface electromyogram electrodes were taped over the belly of the adductor pollicis and on the index finger. A stimulating button electrode was placed over the ulnar nerve at the wrist, and held in position by means of an elastic strap. The indifferent electrode for the stimulator was placed high on the forearm and held in position by sticky tape. Supramaximal ulnar nerve stimulation was ensured by slowly increasing the stimulus voltage until both the surface electromyogram and isometric force had reached a plateau. The stimulus voltage for all subsequent testing was set at 10–20% above this value. The stimulus pulse width was 50 μs. Fatigue of the adductor pollicis was measured by recording the decline in isometric force during repetitive supramaximal tetanic ulnar nerve stimulation. The stimulation protocol consisted of intermittent once per second tetanic stimulation at 40 Hz for 250 ms. During the fatigue protocol the subject was instructed to keep the left hand and forearm as relaxed as possible.

Adductor pollicis fatigue was measured twice in each subject, with a 20 minute rest between measurements. The first was performed with the circulation intact (control fatigue). The second was performed with the circulation occluded by a sphygmomanometer cuff inflated around the upper arm to a value above systolic blood pressure (ischaemic fatigue). Output from the force transducer and from the surface electromyogram was displayed on an oscilloscope, and recorded on a UV chart recorder. The maximum tetanic force of the adductor pollicis was measured as the initial force production at the beginning of the first fatigue protocol. Fatigue was measured as the force production after two minutes of intermittent tetanic stimulation expressed as a percentage of the starting value.

STATISTICAL ANALYSIS

The three groups were compared by analysis of variance. If a significant variation was indicated by the F distribution, further analysis was undertaken with Duncan's test and by the non-parametric Mann-Whitney test. The correlation between quadriceps maximum voluntary contraction and $\dot{V}o_2$ max was assessed by standard linear regression analysis.

Results

All experiments were performed without complication. The quadriceps fatigue protocol was well tolerated. During the adductor pollicis fatigue protocol most subjects found that the ulnar stimulation was uncomfortable but tolerable.

QUADRICEPS: MUSCULAR CONTRACTION

The table shows the results for quadriceps maximum voluntary contraction and fatigue. There was a gradient in the strength of maximum voluntary contraction with the degree of heart failure in the three groups (normal *v* mild chronic heart failure ($p < 0{\cdot}04$), normal *v* severe chronic heart failure ($p < 0{\cdot}01$), and mild chronic heart failure *v* severe chronic heart failure ($p < 0{\cdot}09$). Figure 3 shows the correlation between maximum voluntary contraction and $\dot{V}o_2$ max for the 10 individual patients ($r = 0{\cdot}86, p < 0{\cdot}01$)

QUADRICEPS: FATIGUE

Fatigue in the quadriceps (table) also showed changes relating to the severity of heart failure between the three groups (normal *v* mild chronic heart failure ($p < 0{\cdot}09$), normal *v* severe chronic heart failure ($p < 0{\cdot}01$), and mild chronic heart failure *v* severe chronic heart failure ($p < 0{\cdot}01$). Fatigue in quadriceps correlated with $\dot{V}o_2$ max for the 10 patients with heart failure ($r = 0{\cdot}74, p < 0{\cdot}02$).

QUADRICEPS: TOMOGRAPHY AND HISTOLOGICAL APPEARANCE OF BIOPSY SPECIMENS

The cross sectional area of the quadriceps in the five patients with severe chronic heart failure ranged from 44·7 cm^2 to 53·7 cm^2 (mean 48·2 cm^2). The mean maximum voluntary contraction of quadriceps for the group was 323 N, so the mean force production per unit cross sectional area was 6·7 N/cm^2.

The histological and histochemical examinations showed no consistent abnormality. In two of the subjects with severe chronic heart failure type II fibre atrophy was prominent.

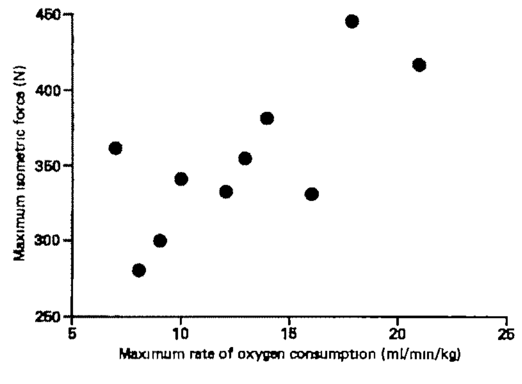


Figure 3 Relation between quadriceps maximum isometric force and maximum rate of oxygen consumption ($\dot{V}o_2$ max) measured during symptom limited treadmill exercise test.

ADDUCTOR POLLICIS: MUSCULAR CONTRACTION

In contrast with the findings for quadriceps there was no significant difference between the maximum isometric force of adductor pollicis in the three groups (table). There was considerable variability between individuals.

ADDUCTOR POLLICIS: FATIGUE

Measurement of fatigue before circulatory occlusion (control fatigue) did not show any significant difference between the three groups. Considerable individual variation in fatigue was apparent. The lowest value for fatigue was found in a patient with severe chronic heart failure. During circulatory occlusion (ischaemic fatigue) all subjects showed a considerable increase in fatigue. There were no statistically significant differences between any of the three groups. Nevertheless, the relative increase in fatigue was significantly greater for those patients with severe chronic heart failure as judged by the ratio of ischaemic to control fatigue (table). The five patients with severe chronic heart failure showed a relatively greater increase in fatigue during circulatory occlusion than the healthy volunteers ($p < 0{\cdot}01$) and patients with mild chronic heart failure ($p < 0{\cdot}01$).

Discussion

Previous work from our laboratory showed significant reduction of muscle strength in the quadriceps of patients with chronic heart failure, which suggested that the reduction of strength may be an important determinant of the reduced exercise tolerance.[11] In the present study we confirmed these findings and showed a correlation between the maximum isometric force of quadriceps and the severity of chronic heart failure assessed by the maximum oxygen consumption on exercise.

In the group of five patients with severe chronic heart failure the maximal isometric force production per unit muscle cross sectional area was $6{\cdot}7$ N/cm^2 which is within the normal range reported by Chapman *et al.*[12] So our results suggest that the reduction of force production seen in the large locomotive muscles of patients with chronic heart failure is due to muscle atrophy and not to impaired force generation by the myofibrils. The cause of the atrophy is unknown but may relate to disuse, repetitive ischaemia linked to reduced blood flow on exercise, or to neural and hormonal factors activated in heart failure.

Histological examination was undertaken in only five patients. The findings were identical with those we reported in a larger study.[11] A wide variety of abnormalities was detected[11] but there was no consistent pattern typical of heart failure. Nor were the findings typical for either rest atrophy or ischaemic induced damage. Findings were similar in the small number of biopsy specimens in the present study. All the patients in the present study had ischaemic heart disease as the cause of heart failure so that histological changes could not be attributed to an undetected myopathy which might be present in patients with idiopathic cardiomyopathy.

A further consideration is the age of the patients. The group of patients with mild heart failure was significantly older than the healthy volunteers (mean difference 21 years ($p < 0{\cdot}03$)) and the patients with severe heart failure (mean difference 13 years ($p < 0{\cdot}04$)). This difference could be of some importance in interpreting the results but is unlikely to be of major significance because there was no significant age difference between the healthy volunteers and patients with severe heart failure (mean difference 8 years). Furthermore, the findings in the patients with mild heart failure were, in general, intermediate between those of the healthy volunteers and the patients with severe heart failure.

In contrast with the findings in the quadriceps, maximum isometric force production of the adductor pollicis revealed no significant difference between healthy volunteers, patients with mild chronic heart failure, and patients with severe chronic heart failure. A possible explanation for this difference between the two muscles is that the use of intrinsic hand muscles (especially in the non-dominant hand) was normal in all three groups. That is to say, patients with chronic heart failure continue to use their hands for everyday activities. In contrast, the limited exercise capacity of patients with chronic heart failure results in disuse atrophy of the large locomotive muscles that contributes to the observed force reduction of the quadriceps.

In physiological terms, muscle fatigue may be defined as an inability to maintain a required level of force production. Though this definition allows for the objective measurement of muscle fatigue, such a measurement is not necessarily synonymous with the symptom of "fatigue" that is so commonly reported by patients with chronic heart failure. Nevertheless, the early onset of muscle fatigue is probably at least a marker of the processes that give rise to the perception of the symptoms of "fatigue". In the present study we showed that objective measurement of quadriceps fatigue correlates with the severity of chronic heart failure as reflected by conventional measurements of maximal exercise capacity (table). In the present studies the level of force production that we used for the quadriceps fatigue protocol was normalised to the invidividual's maximum voluntary contraction. This aspect of our method is important because it made the measurement of fatigue independent of the reduced force development attributable to atrophy. In everyday activities and most functional tests—for example treadmill or bicycle exercise—an absolute level of workload and, therefore, force production is required. In this situation both reduced force production and fatigue will contribute to the subject's impaired exercise capacity.

In contrast with the findings in the quadriceps, the measurement of fatigue in the adductor pollicis under control conditions showed no significant difference between healthy volunteers and patients with mild or severe chronic heart failure. Small muscles might respond differently to the altered neurohormonal control of blood flow in heart failure or be less susceptible to changes in the microvasculature. Perhaps the most probable explanation is related to blood flow. Activation of a large muscle mass results in a greatly reduced skeletal muscle blood flow in patients with chronic heart failure.[4] This reduced skeletal muscle blood flow is a major factor responsible for the observed increase in fatigue of the quadriceps in patients with chronic heart failure. In contrast, the adductor pollicis is a small intrinsic hand muscle and even during maximal activation the required increase in blood flow is a small proportion of the cardiac output even when chronic heart failure is severe. The last hypothesis does not accord with the idea that in severe chronic heart failure there is a generalised intrinsic abnormality of the microcirculation with skeletal muscle, such that normal vasodilatation cannot occur.[13]

The effect of circulatory occlusion on the development of fatigue in the adductor pollicis is more difficult to interpret. During the measurement of fatigue in the adductor pollicis under control conditions there were significant differences between the three groups. After circulatory occlusion all subjects showed a considerable increase in fatigue (as expected) but there was still no statistically significant difference among the three groups. The relative increase in fatigue after circulatory occlusion, however, was significantly greater in the patients with severe chronic heart failure. This relative increase in fatigue may be partly due to a degree of fatigue resistance under control conditions and partly a tendency towards increased fatigability after circulatory occlusion in the patients with severe chronic heart failure. An explanation for the relative increase in fatigue in the adductor pollicis after circulatory occlusion in patients with severe chronic heart failure is that there is an intrinsic alteration in skeletal muscle function which has previously been suggested in studies with magnetic resonance spectroscopy.[6 7] Within the skeletal muscle fibres of the adductor pollicis in patients with severe chronic heart failure there could be a relative shift from glycolytic to oxidative metabolic pathways for energy production combined with a reduction in myosin ATPase activity, such that the muscle fibres become relatively fatigue resistant.

The present study shows that patients with chronic heart failure show both atrophy and weakness of the large locomotive muscles. In addition, these muscles show increased fatigue, the magnitude of which correlates with the severity of chronic heart failure. The mechanism of the increased fatigue in the large locomotive muscles is possibly related to an absolute reduction in skeletal muscle blood flow. The results from the adductor pollicis suggest that muscle weakness is not an inevitable consequence of chronic heart failure, but instead supports the concept that disuse atrophy is responsible for the observed weakness of the quadriceps. The similar values for fatigue of the adductor pollicis in the three groups suggest that skeletal muscle blood flow can increase normally as long as the activated muscle mass is small. The observation of a relatively greater increase of fatigue of the adductor pollicis during circulatory occlusion in patients with severe chronic heart failure supports the hypothesis that there is an intrinsic alteration in skeletal muscle metabolism in these patients.

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Cardiac metabolism during exercise in healthy volunteers measured by ^{31}P magnetic resonance spectroscopy

Michael A Conway, J David Bristow, Martin J Blackledge, Bheeshma Rajagopalan, George K Radda

Abstract

A technique was devised for individuals to exercise prone in a magnet during magnetic resonance spectroscopy of the heart and phosphorus-31 magnetic resonance spectra of the heart were obtained by the phase modulated rotating frame imaging technique in six healthy volunteers during steady state dynamic quadriceps exercise. During prone exercise heart rate, blood pressure, and total body oxygen consumption were measured at increasing loads and the results were compared with those during Bruce protocol treadmill exercise. During prone exercise with a 5 kg load the heart rate was similar and the systolic and diastolic blood pressures were higher than those during stage 1 of the Bruce protocol. The rate-pressure products were similar but the total body oxygen consumption was lower during prone exercise. There was no difference in the ratio of phosphocreatine to adenosine triphosphate during rest and exercise.

Thus during exercise that produced a local cardiac stress equal to or greater than that during stage 1 of the Bruce protocol treadmill exercise, the energy requirements of the normal human myocardium were adequately supplied by oxidative phosphorylation.

The relation between energy provision and mechanical function of the myocardium in healthy and diseased states is fundamental to cardiology. Over the past decade, phosphorus-31 magnetic resonance spectroscopy has been shown to be a powerful tool for the study of tissue energetics in isolated perfused rodent hearts.[1] The technique has also been applied in surgically exposed animal hearts.[2-4] The relations between the concentrations of high energy phosphate compounds such as phosphocreatine and adenosine triphosphate and intracellular pH and mechanical function during ischaemia and reperfusion as well as the effects of abnormal endocrine function such as hyperthyroidism have been extensively studied.[5 6]

More recently, the development of large bore magnets has enabled phosphorus spectra of the human heart to be obtained non-invasively in healthy volunteers at rest.[7-9] The addition of proton decoupling improved the resolution of the phosphorus spectra.[10] Some success has been achieved in obtaining spectra of hearts of patients with hypertrophic cardiomyopathies and myocardial infarction at rest.[11 12] No striking abnormalities were seen in the concentrations of high energy phosphates in the hearts of patients with cardiomyopathies.[11] This accords with the observation that other methods of cardiac assessment do not show abnormalities of function when the patient is studied at rest. Many indices of cardiac function are abnormal when the patient is stressed. To obtain phosphorus-31 magnetic resonance spectra of the human heart during exercise, an exercise stress test for use in whole body magnets is required. Exercising in the confined space of a magnet is difficult. The subject is required to lie face down (to reduce the distance between the coil and the myocardium) with the heart in the middle of the homogeneous magnetic field of a 60 cm bore tube. Movement of the thorax must be minimal to ensure accurate localisation. Because it takes 15–30 minutes to obtain a phosphorus-13 spectroscopic image of the heart, the patient must be able to maintain a steady level of exercise for this period.

To overcome these difficulties we developed a new exercise machine and protocol of prone exercise (pronex) in which the subjects lie face down in the bore of the magnet with the chest immobilised over the spectroscopy probe and exercise by extending their foreleg. We measured heart rate, blood pressure, rate-pressure products, and total body oxygen consumption at different workloads and compared these results with the measurements in the same individuals during the standard Bruce protocol treadmill test. We then obtained phosphorus-31 spectra from the hearts of five individuals at rest and during one level of prone exercise. An outline of the results was reported in a letter to the *Lancet*.[13] We compared the results of physiological measurements during stage 2 of prone exercise and stage 1 of the Bruce protocol in six healthy volunteers and measured the ratio of phosphocreatine to adenosine triphosphate by magnetic resonance in five.[13]

In the present paper we report the physiological response at different levels of exercise and the spatially resolved spectra in the same six healthy volunteers. We also studied seven more individuals to determine the reproducibility and steady state response during prone exercise.

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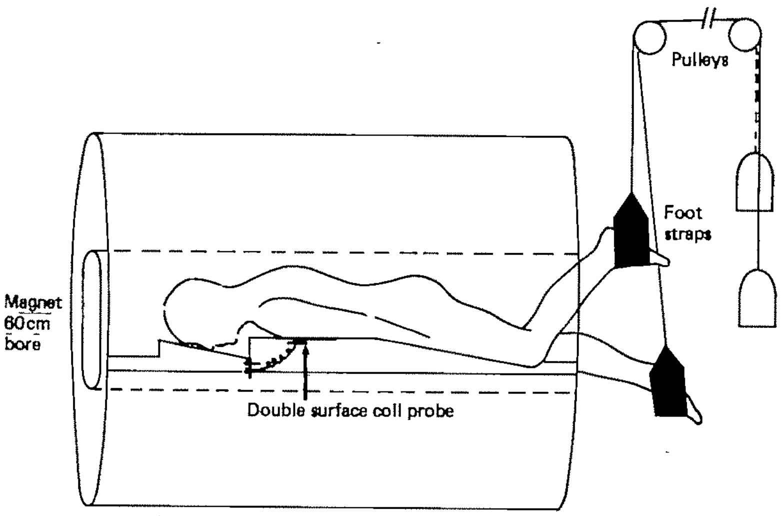

Figure 1 Arrangement for prone exercise in the bore of a horizontal magnet. The heart lies in the middle of the homogeneous field. Each foot is suspended in a strap connected to a 5 kg weight via a cable.

Subjects and methods

The studies were performed in two stages. Preliminary assessments were made in the exercise laboratory on a specially constructed rig, with a similar design to the machine that was attached to the magnet (fig 1). The rig consisted of an A frame (180 cm by 100 cm by 80 cm) to which pulleys were attached and a modified examination couch. Cylinders were used for weights and the load was increased by adding water from reservoirs attached to the apex of the A frame. The subject lay prone on the couch with each foot in a separate strap suspended on a cable. This position corresponded to that in the bore of the magnet and provided ideal stability of the thorax.

EXPERIMENTAL PROTOCOL

Individuals were examined and weighed. Then they lay on a mat and the approximate weight of each foreleg was measured by small scales. The subject then climbed on to the couch and was connected to the machine. They gripped a Lloyd respiratory valve in their mouth; a nose clip was applied; and a three minute sample of resting expired air was collected in a Douglas bag. The subject rested for five minutes and the heart rate and blood pressure were measured from a monitor (Cardiac Recorders) and manual sphygmomanometer. To record blood pressure the left arm was abducted and supported on a frame at an angle of approximately 45° from the horizontal. After collection of the resting expirate exercise started. Individuals moved their forelegs in time to a metronome set at 100 per minute such that each leg moved fifty times per minute. The weights were raised approximately 25 cm with each leg extension. The subjects were asked to hold the weights suspended just above the floor at the end of each relaxation. Expired air was collected during the third, eleventh, and nineteenth minutes of exercise. Subjects lifted 2·5 kg during the first three minutes, which was equivalent to the estimated weight of the right forelimb in most individuals. This was increased by 1·25 kg during the fourth, eighth, twelfth, and sixteenth minutes of exercise such that during collection of the second and third samples of expired air the workloads were 5 kg and 7·5 kg respectively. The samples of expirate were kept sealed in the Douglas bags until the end of the experiment. A 30 ml sample of the expired air was then drawn into a glass syringe and the volume of air in the bags was measured with a dry gas meter (Parkinson Cowan). These samples were then analysed for oxygen, nitrogen, and carbon dioxide by a mass spectrometer (Centronics). Oxygen consumption was calculated from the Haldane equation with adjustments for the prevailing barometric pressure, temperature, and nitrogen and oxygen concentrations in room air.

The same six individuals also performed treadmill exercise according to the Bruce protocol on a separate day. Blood pressure and heart rate were recorded every minute and the total body oxygen consumption was measured by the above procedure from samples of expired air collected during the third minute of each of stages 1 to 4. The steady state response and reproducibility of the changes during prone exercise were assessed in four and five of the seven extra subjects respectively.

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy was performed with a 1·9 T, 60 cm bore superconducting magnet (Oxford Instruments) interfaced with a Fourier transform spectrometer (Bruker) operating at frequencies of 32·701 and 80·783 MHz for ^{31}P and ^{1}H respectively. The phase modulated rotating frame imaging technique that we used for spectroscopy has been described elsewhere.[14] Recordings were made from the subject lying prone with the heart positioned over a double concentric surface coil (transmitter diameter 15 cm and receiver diameter 6·5 cm). We used the proton signal to optimise the magnetic field homogeneity ("shimming"). Phosphorus-31 spectroscopic images were collected from the anterior aspects of the right and left ventricles and adjacent septum by acquiring two datasets, each consisting of 16 incremental pulse widths of 16 scans at a repetition rate of 3 seconds (total time per image = 28 minutes). We used pulse sequence:

$$n\Delta\theta \pm x - \lambda y - \text{Aq} - \text{Delay}$$

where n is the number of the increment, $\Delta\theta$ the length of the pulse, λ the phase encoding pulse (optimally $\pi/2$ at sample centre), and Aq, the acquisition time (0·512 s). In our experiments (using 140 W radiofrequency transmitter power) both $\Delta\theta$ and λ were set at 350 μs. The distance was calibrated from phantom experiments and by this protocol the spatial resolution at half height of the technique was estimated to be 5–6 mm. Spectra from the heart were identified from the plateau in the ratio of phosphocreatine to adenosine triphosphate as described else-

Table 1 *Data on main subject population at rest and upright*

No	*Age (yr)*	*Wt (kg)*	*Heart rate (beats/min)*	*SBP/DBP (mm Hg)*	*$\dot{V}O_2$ (ml/kg/min)*
1	26	73	84	112/68	3·7
2	25	65	53	110/74	4 1
3	24	66	58	122/76	4·2
4	25	64	45	110/70	4 0
5	24	71	52	120/74	4·0
6	28	73	74	108/74	3·0

Mean variables among other subjects also used for steady state and reproducibility studies (mean (SD))

n	*Age*	*Wt (kg)*	*Heart rate (beats/min)*	*SBP*	*DBP*	*$\dot{V}O_2$*
7	40 (8)	74 (5)	72 (6)	123 (4)	75 (9)	3 6 (0·3)

SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_2$, total body oxygen consumption.

where.[14] The peaks in the spectra were measured by triangulation of the areas under the phosphocreatine and γ adenosine triphosphate peaks. We expressed the results as ratios because the measurement of absolute concentrations of metabolites by surface coils is not yet possible.[15] In any case, the ratio of phosphocreatine to adenosine triphosphate adequately expresses the energy state of heart muscle.[16] The measurement of myocardial pH in vivo requires the identification of the signal from intracellular inorganic phosphate. Unfortunately, in vivo the peaks of 2–3 diphosphoglycerate from red blood cells and extracellular inorganic phosphate overlap with the intracellular inorganic phosphate, so that with current techniques pH cannot be measured.[17 18] Because a value for pH is necessary for the calculation of free adenosine diphosphate from the creatine kinase equilibrium, we could not calculate free adenosine diphosphate values.

Subjects exercised in the magnet using the arrangement shown in fig 1. The subject lay prone on the probe with the forelegs protruding from the bore of the magnet. Each foot was attached to a strap and a stainless steel cable. The latter was connected via pulleys (suspended on aluminium uprights bolted to the magnet) to brass weights that were attached to the wall of the magnet room. The end of the magnet was enclosed in a Faraday cage to avoid the introduction of noise into the spectrometer by external sources of radiofrequency.

Table 2 *Physiological changes (mean (SD)) during incremental prone exercise and treadmill exercise in six individuals*

	Heart rate (beats/min)	*SBP (mm Hg)*	*DBP (mm Hg)*	*$\dot{V}O_2$ (ml/kg/min)*
		Pronex		
Rest	58 (10)	124 (8)	84 (8)	3·6 (0·4)
Stage 1	73 (20)	129 (8)	92 (5)	6 0 (0·2)
Stage 2	86 (19)	146 (16)	100 (6)	9·2 (2 0)
Stage 3	119 (30)	172 (22)	116 (11)	13 3 (2·1)
		Treadmill		
Rest	58 (15)	114 (6)	73 (3)	3·8 (0·4)
Stage 1	91 (15)	134 (17)	73 (6)	14·5 (2·9)
Stage 2	103 (16)	147 (20)	70 (6)	18·9 (2·8)
Stage 3	137 (15)	158 (26)	68 (6)	26·7 (4·1)
Stage 4	168 (20)	162 (30)	67 (13)	35 1 (5 4)

See footnote to table 1 for abbreviations.

Once the resting spectra had been collected the subject exercised for two minutes while the shimming was rechecked. (The subjects were not removed from the magnet between the rest and exercise recordings.) Spectra were then collected throughout the remaining 28 minutes of exercise. The workload was 5 kg and the rate of pulling was 50 per minute per leg. Heart rate and cardiac rhythm were monitored electrocardiographically by electrodes attached to the abdominal wall.

SUBJECTS

The main study was performed on six men who were drawn from the 13 subjects who participated in the physiological characterisation and assessment of the reproducibility of prone exercise. All were healthy and had no symptoms or signs of cardiac disease. Table 1 shows the cardiorespiratory variables in upright resting subjects. All subjects consented to the study which was approved by the local ethics committee. Statistical analysis was performed by analysis of variance and Student's t test.

Results

The results of the measurements performed in the five main parts of the study are shown below—that is, the physiological changes during incremental prone exercise, during Bruce protocol treadmill exercise, during steady state prone exercise, and during the reproducibility studies. The spectra from the myocardium at rest were then compared with those during prone exercise in five men.

PHYSIOLOGICAL CHANGES DURING PRONE AND TREADMILL EXERCISE

Table 2 shows heart rate, blood pressure, and total body oxygen consumption in six men lying prone at rest and during two exercise protocols. Systolic and diastolic blood pressures (mm Hg) were higher in the prone position at rest than in the upright position (114 (6)/73 (3) v 124 (8)/84 (8); $p < 0{\cdot}02$). The resting heart rate was similar in both the upright and prone positions. The mean value for the heart rate at stage 3 of the prone exercise was intermediate between stage 2 and stage 3 of the Bruce protocol. The mean systolic blood pressures at each stage were only slightly higher during treadmill exercise. There was a considerable difference in the response of the diastolic blood pressure. This fell during treadmill exercise whereas the higher resting dias-

Table 3 *Rate-pressure product (mean (SD)) during pronex and treadmill exercise in six healthy individuals*

	Pronex	*Treadmill*
Rest	7267 (1389)	6916 (1606)
Stage 1	9461 (2852)	12290 (3028)*
Stage 2	12670 (3580)*	15810 (4088)
Stage 3	20569 (6992)	22287 (5273)
Stage 4		22459 (6880)

*NS.

Table 4 Steady state prone exercise (mean (SD)) results in four of seven healthy individuals

Variable	*Rest*	*3 min*	*11 min*	*19 min*
HR	76 (12)	90 (13)*	91 (15)*	91 (13)*
SBP	126 (6)	145 (3)*	140 (5)*	144 (4)*
DBP	81 (6)	92 (3)*	93 (4)*	92 (3)*
$\dot{V}o_2$	3·4 (0 3)	7 8 (0 9)*	8 8 (1 8)*	8·4 (1·2)*

*None of the variables changed significantly during the pronex test.
HR, heart rate. See footnote to table 1 for other abbreviations

Table 5 Reproducibility of the prone exercise protocol (mean (SD)) in five of seven healthy individuals

Variable	*Rest 1*	*Rest 2*	*Exercise 1*	*Exercise 2*
HR	65 (12)	63 (13)	86 (21)	82 (19)
SBP	120 (9)	121 (7)	132 (14)	133 (14)
DBP	83 (8)	84 (8)	89 (8)	93 (5)
$\dot{V}o_2$	3 38 (0 16)	3 43 (0 22)	7 95 (1 66)	7 4 (1 2)

See footnote to table 1 for abbreviations.

tolic blood pressure rose as the workload was increased during prone exercise. The difference in the diastolic blood pressure between both types of exercise was highly significant ($p < 0·0001$).

The oxygen consumption was equivalent at rest before both types of exercise and was similar to the normal values reported by other investigators.[19] During treadmill exercise the oxygen consumption was slightly lower at each stage than that reported elsewhere. The oxygen consumption at stage 3 of the prone exercise was similar to that at stage 1 of the Bruce protocol.

Table 3 shows the rate-pressure products of the two types of exercise. They show that high rate-pressure products can be achieved during prone exercise. Indeed during the final stage of the prone exercise protocol the rate-pressure product was over 20 000 and was close to those during stages 3 and 4 of the Bruce protocol.

PHYSIOLOGICAL CHANGES DURING STEADY STATE PRONE EXERCISE

The changes in the oxygen consumption and haemodynamic variables in four subjects exercising at constant workload (5 kg) for 20 minutes were studied to determine the variability of the response to prone exercise (table 4). Whole body metabolism was in a reasonably steady state throughout the exercise (3 min *v* 11 min *v* 19 min) indicating that the magnetic resonance spectra were obtained during steady state cardiac metabolism.

REPRODUCIBILITY OF PHYSIOLOGICAL MEASUREMENTS

Reproducibility of the measurements was examined by measuring the haemodynamic variables at rest and during exercise on two separate days within a six week period (table 5).

MAGNETIC RESONANCE SPECTROSCOPY

Spectra from the myocardium were successfully recorded in five of the six subjects. The signal to noise in the spectra from the sixth subject was not adequate for analysis because of the large distance between the myocardium and the probe. Figure 2 shows typical spectra at rest from one of the subjects. (These are comparable to the spectra acquired from this subject 3 years ago.)[14] The ratio of the phosphocreatine to adenosine triphosphate at rest was similar to that in the spectra recorded in the subject during 28 minutes of steady state exercise. The mean ratio of phosphocreatine to adenosine triphosphate in the five subjects at rest (1·5 (0·2); mean (SD)) was not significantly different from that during exercise (1·58 (0·14)). The workload (5 kg) used during stage 2 of the incremental prone exercise was used for the exercise during spectroscopy. This level of work was chosen because it could be sustained during the period required for data acquisition. It caused an approximate threefold increase in total body oxygen consumption and a rate-pressure product that was similar to that at stage 1 of the Bruce protocol.

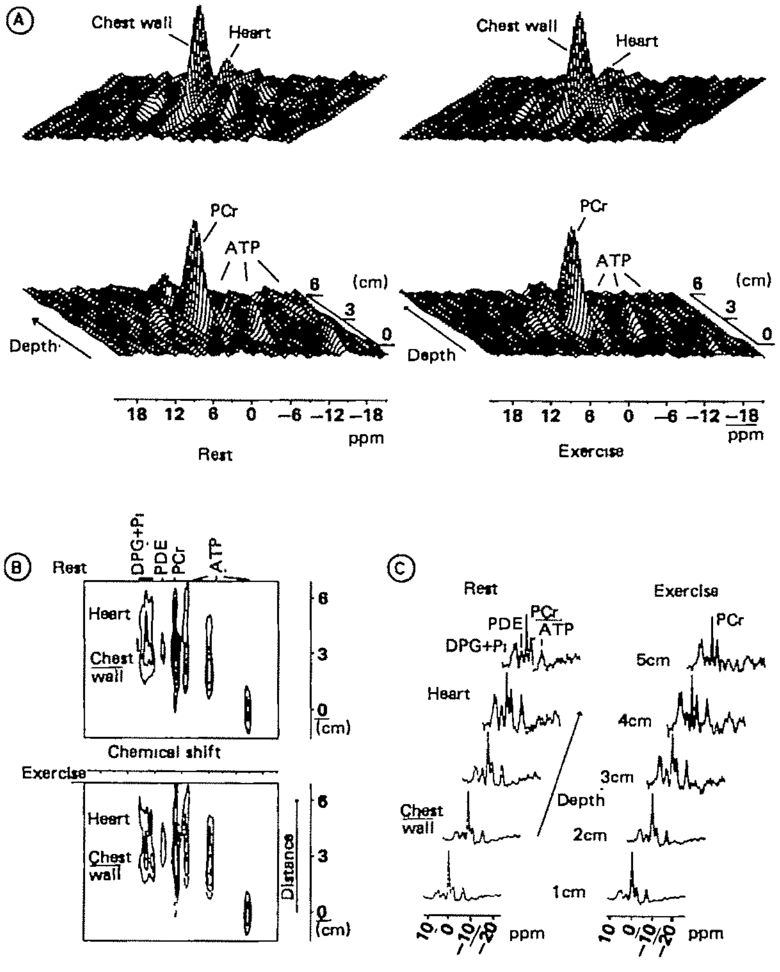

Figure 2 (A) Double projection stack plots of phase modulated images of the chest wall and heart at rest and during exercise obtained by the rotating frame technique. The heart is clearly seen in the deeper regions of the image. (B) The corresponding contour plots of the rest and exercise study which allow identification of the heart in the deeper regions. (C) The spectra were selected from corresponding rows in each image. Pi, inorganic phosphate; DPG, diphosphoglycerate; PCr, phosphocreatine; ATP, adenosine triphosphate; PDE, phosphodiester.

Discussion

This study was designed to evaluate a new technique of exercise for study of the human heart and to describe the pattern of phosphorus-31 magnetic resonance spectra during light exercise in healthy volunteers.

The constraints of the spectroscopy technique require the development of methods of exercise suitable for studies of individuals lying prone and in a fixed position that are applicable in patients with myocardial disease. Several methods of exercise and other stress techniques could have been attempted. A modification of the arm crank exercise[20] is possible but is less suitable because of the smaller muscle bulk and movement of the upper thorax. Supine bicycle ergometry is also unsatisfactory because in this position the myocardium is furthest away from the surface coil. The need for a long recording time precludes magnetic resonance spectroscopy after exercise outside the magnet, and sustained isometric exercise over long periods is exhausting.[21] Though pacing[22] and pharmacological stimulation[23-25] could be used to solve the technical problems associated with movement they are at best a close approximation to the physiological response to exercise.

Prone dynamic exercise of the quadriceps muscles solves most of the problems associated with exercise in horizontal magnets and the haemodynamic changes elicited meant that this was a good method of applying a local cardiac stress with low level muscular exercise. This type of exercise does not seem to have been studied before. Treadmill and upright bicycle ergometry have been evaluated extensively[19 26] and several investigators have examined the physiological changes during supine bicycle ergometry.[27] In contrast with the findings in these types of exercise there was an unusually large rise in the diastolic blood pressure in all the subjects during prone exercise. The rate-pressure product is similar to that during the treadmill test. In contrast, total body oxygen consumption is lower in prone exercise. Because for each individual the rate-pressure product is almost linearly related to myocardial oxygen consumption,[28] these results suggest that the same myocardial stress can be achieved at a lower total body oxygen consumption during our prone exercise protocol.

A diastolic blood pressure of > 120 mm Hg was recorded in several subjects during the final stage of prone incremental exercise. This pressure is similar to those reported in some subjects during isometric exercise.[21] The isometric exercise is probably performed by the hamstrings because the subject is required to hold the weight suspended in the weight carrier between each elevation. The back muscles also perform isometric exercise in stabilising the pelvis. A further factor that may be relevant to the increase in cardiac work is the change in blood volume distribution. Cardiac volume is greater during horizontal supine exercise[29] and though lying on the chest may affect intrathoracic pressures, some increase in cardiac volume is likely. The workloads that we used in the present protocol were derived from the weight of the forelegs. This was initially determined for each leg by filling the cylinder until its weight exactly balanced that of the prone foreleg and caused the leg to flex. The weight was similarly estimated by resting the prone foreleg (at the instep) on small scales. Most subjects registered 2·5 kg for the right leg and so this was used as the initial workload. All the subjects were able to perform exercise at the 5 kg workload for the required length of time without interruption.

Magnetic resonance spectroscopy was performed without cardiac or respiratory gating. Thus the measurements are the mean of systole and diastole. Comparison of systolic and diastolic measurements of phosphorus metabolites in beating animal hearts[30] did not show any differences between the phases of the cardiac cycle; and spectra collected from human hearts by the phase modulated rotating frame imaging technique in parallel studies were not altered by gating. The sensitive volume of the probe used in these studies is a cylinder coaxial with the probe whose diameter is the same as that of the receiver coil (6·5 cm) and increases by about 25% at a depth of 5–6 cm. With this configuration and the position of the probe as determined by echocardiograms, only the heart is seen by the probe. Moreover, if the diaphragm had been included in the sampled volume, because skeletal muscle has a high ratio of phosphocreatine to adenosine triphosphate, the images would have shown higher ratios than were detected.

Measurements of the ratio of phosphocreatine to adenosine triphosphate are used as a measure of energy metabolism. Absolute values for these metabolites cannot be derived accurately with current technology. This is because the sensitivity of the surface coils has a complex shape and varies in space depending on various factors such as electrical loading by the tissues.[15] These factors have not yet been elucidated in sufficient detail for absolute concentrations to be estimated. The presence of a large peak for the 2,3 diphosphoglycerate in blood at the frequency of the inorganic phosphate interferes with the measurement of pH.

The ratio of phosphocreatine to adenosine triphosphate was no different during rest and exercise. The absence of change in this ratio during exercise suggests that the energy requirements of the heart are adequately supplied by oxidative phosphorylation during light exercise. This indicates that during ordinary increases in exertion such as walking or light running myocardial metabolism is solely oxidative and phosphocreatine is not broken down. In the skeletal muscle of healthy individuals there was little change in phosphocreatine and pH fell during light exercise.[31]

The metabolism of the diseased myocardium during exercise has not been studied yet. It is likely that there are considerable changes in phosphocreatine resembling the abnormalities in the skeletal muscle of patients with heart failure.[31] Prone exercise should be an efficient method of studying the ischaemic myocardium because a large local haemodynamic stress can be produced by relatively low muscular effort. The applicability of the exercise technique in middle aged patients has already been examined. The level of exercise can be tailored to each individual and significant changes in haemodynamic variables would be expected with workloads as low as 2·0–2·5 kg. Exercise magnetic resonance spectroscopy studies will require adequate cardiac monitoring with the electrocardiograph to detect arrhythmias and ST/T wave changes. This is difficult at present because of the large electrical artefacts caused by blood flow and movement of leads in the high magnetic fields needed for spectroscopy.

In conclusion, phosphorus-31 magnetic resonance spectra were recorded from the normal myocardium during exercise during a new exercise protocol. There were no differences in high energy phosphorus metabolism during light steady state exercise, which suggests that the normal myocardium is adequately supplied by oxidative metabolism during exercise.

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An echocardiographic assessment of atrial mechanical behaviour

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Abstract

Relations between movement of the atrioventricular ring and changes in left atrial and ventricular dimensions were studied by echocardiography and compared with apexcardiography and Doppler mitral flow velocity traces in 20 healthy controls and in patients with left ventricular hypertrophy ($n = 28$) or dilatation ($n = 16$). During left ventricular systole the atrioventricular ring, a structure common to ventricle and atrium, moved towards the ventricular apex, thus increasing left atrial volume. This action matched pulmonary venous return because it was in phase with the transverse left atrial dimension measured from aortic root to posterior left atrial wall. During early diastole, the mitral ring moved rapidly towards the atrium as transmitral flow accelerated. This requires a force directed from ventricle to atrium, likely to be the result of elastic recoil arising from compression of the ventricular myocardium or stretching of the atrial myocardium during ventricular systole. Two additional mechanisms of ventricular filling with atrial systole were recognised: (*a*) an increase in ventricular volume as the atrioventricular ring moved upwards and (*b*) transverse left ventricular expansion by pressure driven transmitral flow. The former is undetectable by Doppler from the apex; it accounted for 10% of ventricular filling in the healthy controls, but for significantly less in those with ventricular dilatation. In left ventricular hypertrophy, left ventricular filling was maintained by both mechanisms compensating for the reduced increase in volume early in diastole.

Interactions between the atrium and ventricle are functionally important during ventricular systole, early diastole, and in atrial systole. They are not included in the traditional separation of atrial function into reservoir, conduit, and pump functions.

In many patients with ventricular disease standard clinical investigations showed increased atrial contractile activity.[1-3] This almost certainly represents a mechanism by which ventricular function is optimised,[4] and presumably it develops because of information transferred from a diseased ventricle to the corresponding atrium. The mechanism of such an interaction remains unknown. Standard descriptions of atrial function do not invoke any influence of either systolic or diastolic ventricular function,[5-7] neither do they explain why increased atrial activity in apparently similar patients may give rise to different changes in atrial pressures or flow rates. We have attempted to understand these processes by the study of atrial and ventricular wall motion during diastole and its relation to atrial pressure and flow rate, which we assessed by simple non-invasive techniques in healthy controls and patients with ventricular disease.

Patients and methods

PATIENTS

M mode echocardiograms, Doppler echocardiographic mitral velocity traces, and apexcardiograms were obtained in 28 patients with left ventricular hypertrophy and 16 with dilated cardiomyopathy and sinus rhythm. We also studied 20 healthy controls (aged 53 (12) years) with normal amplitude and timing of ventricular wall motion on minor axis echocardiography.

Patients with left ventricular hypertrophy had end diastolic septal or posterior wall thickness > 12 mm (upper limit of normal) on M mode echocardiography.[8] Three of these patients had hypertrophic cardiomyopathy; of the remainder with secondary hypertrophy, seven had aortic stenosis, 15 arterial hypertension, two had undergone aortic valve replacement, and one repair of coarctation.

All patients with dilated cardiomyopathy had increased left ventricular end diastolic ($> 5{\cdot}5$ cm) and end systolic dimensions (> 4 cm) and fractional shortening below 23%, the lower limit of the 95% confidence interval in our healthy controls. In nine patients the diagnosis was coronary artery disease; the remainder had idiopathic cardiomyopathy. Seven had mild functional mitral regurgitation detected by Doppler echocardiography.

METHODS

We obtained M mode and cross sectional echocardiograms with the patient lying in the left lateral position. We used an Advanced Technical Laboratory 860C imager equipped with a 3·5 MHz mechanical transducer. M mode echocardiograms, Doppler mitral velocity traces, and apexcardiograms were recorded separately on a Honeywell (Ecoline 22) strip chart recorder at a paper speed of

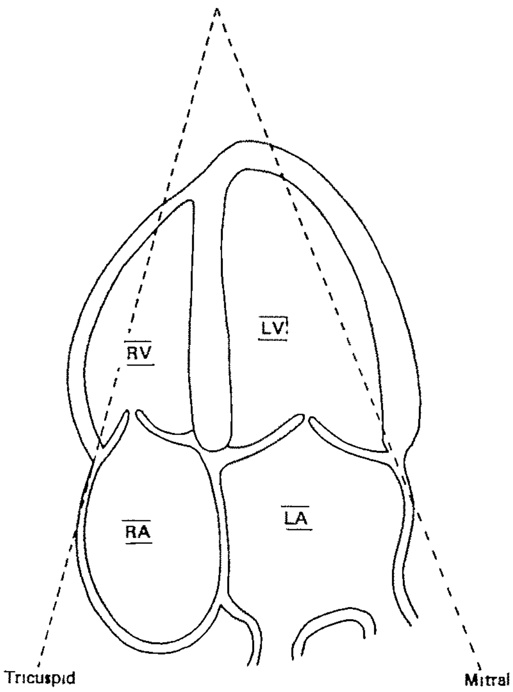

Figure 1 Drawing of apical four chamber cross sectional view showing the M mode cursor positioned through the anterior tricuspid ring and the posterior mitral ring. Movements of the atrioventricular ring reflect changes in long axis dimensions of atria and ventricles.

100 mm/s with simultaneous electrocardiogram and phonocardiogram.

Standard M mode echocardiograms of the left ventricular minor axis were recorded at the level of the mitral leaflet. Because movements of the base of the heart reflect changes in atrial and ventricular volumes we also obtained M mode echocardiograms of the atrioventricular ring after longitudinal placement of a cursor through the anterior tricuspid and posterior mitral valve rings, visualised on the apical four chamber view (fig 1). We compared mitral ring movement with changes in the anteroposterior left atrial dimension assessed from cross sectionally guided M mode echocardiograms at aortic valve level. A good quality Doppler signal representing mitral diastolic velocity was obtained from the cardiac apex by a Doptek system with 2 MHz transducer and was recorded with frequency shift calibration. The apexcardiogram was separately recorded.

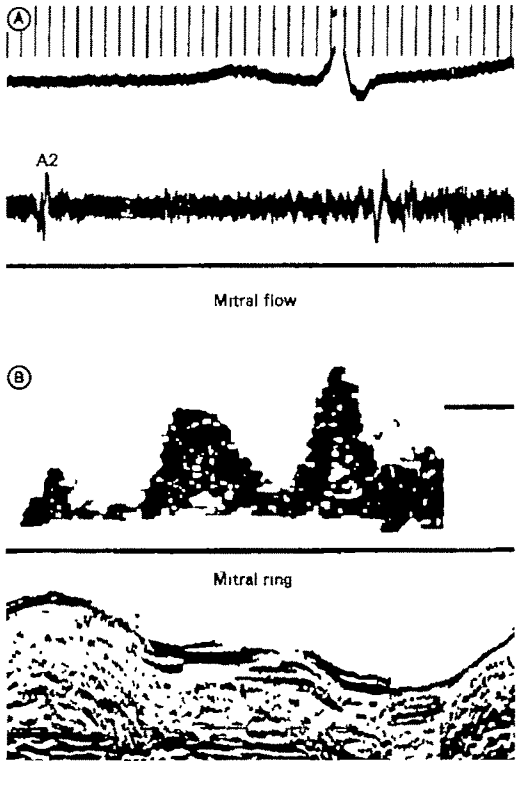

Figure 2 Two components of diastolic left ventricular filling superimposed from matched beats in the same patient. (A) Doppler mitral flow velocity trace and (B) motion of mitral ring towards the left atrium representing expansion of the left ventricular long axis. The effective mitral valve area is deemed to be the same for each mechanism.

All recordings were matched for heart rate. The echocardiograms were digitised and the following measurements were taken:

Atrioventricular ring and posterior aortic root
(*a*) Extent and direction of movement during ventricular systole (cm).
(*b*) Extent, direction, and peak velocity of movement in early diastole (cm, cm/s).
(*c*) Extent and direction of movement during atrial systole (cm); the extent is also expressed as a proportion of the total excursion (%).
(*d*) Transverse left atrial dimensions at end diastole (Q wave) and end systole (mitral valve opening) (cm).

Transmitral flow velocity
(*a*) Peak velocity during early diastole (m/s).
(*b*) Peak velocity during atrial systole (m/s).
(*c*) Time integrals, defined as the areas beneath the velocity curves, during early diastole and atrial systole (cm).

Apexcardiogram
(*a*) 'a' wave amplitude, expressed as a proportion of the total amplitude (%).

Left ventricular minor axis echocardiogram
(*a*) Isovolumic relaxation time defined as the interval from aortic valve closure to mitral valve opening.
(*b*) Peak rate of dimension change in diastole (cm/s) as a proportion of the total increase (%).
(*c*) Dimension change during atrial systole expressed as a proportion of the total increase (%).
(*d*) Septal and posterior wall thickness (cm).
(*e*) Peak rate of posterior thinning (cm/s).
(*f*) Fractional shortening.

During diastole the greater part of the blood volume expanding the left ventricle may be calculated as the product of the time integral of the mitral velocity trace, dimensionally equivalent to a distance, and the effective mitral valve area. A smaller volume of blood enters the ventricle because the mitral ring is carried back over it as the long axis expands (fig 2). This volume is the product of the mitral ring displacement during filling and the mitral valve area because the effective valve area is the same for both components of the volume increase. The component due to mitral ring movement does not involve movement of blood and so is unlikely to be detected by Doppler echocardiography. The ratio of mitral ring displacement to the time integral of mitral velocity alone represents the ratio of long axis ventricular filling to the remainder, and was calculated in all patients during early and late diastole.

All results were expressed as the mean (1 SD). The significance of the differences between means in the different groups was tested by unpaired *t* tests.

Table 1 Atrioventricular ring movement (mean (1 SD))

	Controls	*Left ventricular hypertrophy*	*Left ventricular dilatation*
Ventricular systole.			
Onset mitral (ms)	80 (40)	110 (35)	125 (85)
Onset tricuspid (ms)	50 (20)	70 (40)	55 (50)
Excursion mitral (cm)	1·4 (0·3)	1·2 (0·3)	0·7 (0·2)†
Excursion tricuspid (cm)	2·6 (0·5)	2·3 (0·4)	1·6 (0·6)†
Early diastole			
Velocity mitral (cm/s)	7·0 (3·0)	5·0 (1·7)†	5·0 (2·0)*
Velocity tricuspid (cm/s)	8·0 (3·0)	8·5 (2·4)	11·0 (4·0)†
Excursion mitral (cm)	0·7 (0·2)	0·5 (0·3)*	0·4 (0·2)†
Excursion tricuspid (cm)	1·1 (0·4)	1·1 (0·3)	0·9 (0·6)
Atrial systole			
Excursion mitral (cm) (%)	0·6 (0·2) (40 (16))	0·7 (0·2) (50 (12)*)	0·3 (0·2)† (28 (15)†)
Excursion tricuspid (cm) (%)	1·0 (0·4) (43 (14))	1·1 (0·4) (46 (14))	0·4 (0·40)† (37 (24))

*p < 0·05 and †p < 0·01 compared with controls.

Results

CONTROLS

Movement of the atrioventricular ring (table 1).—The atrioventricular ring moved down towards the ventricles throughout ventricular systole and up towards the atria during early diastole and atrial systole, with a pause during mid-diastole. The tricuspid ring moved further than the mitral ring during both ventricular and atrial systole (ventricular systole 2·6 (0·5) *v* 1·4 (0·3) cm, p < 0·01; atrial systole 1 (0·4) *v* 0·6 (0·2) cm, p < 0·01). But as a proportion of the total movement, atrial systole caused similar upward displacement of the right and left sides. Mitral ring excursion was responsible for 8 (2·1)% of the total increase in left ventricular volume during early diastole and 10 (3·9)% of the total during atrial systole.

Anteroposterior left atrial dimension (table 2).—The anteroposterior dimension increased during ventricular systole reaching a peak with mitral valve opening, and fell during diastole. These changes were less than those of the mitral ring during ventricular systole (1 (0·2) *v* 1·4 (0·3) cm, p < 0·01) and early diastole (0·5 (0·1) *v* 0·7 (0·2) cm, p < 0·05). During atrial systole anteroposterior change and mitral ring excursion were similar (both 0·6 (0·2) cm). Movements were effectively synchronous throughout the cardiac cycle, with that of the mitral ring preceding the anteroposterior axis by 5 (10) ms at its onset, 25 (50) ms at its peak, and 10 (50) ms at the onset of atrial systole (all NS).

Table 2 Anteroposterior left atrial dimension (mean (1 SD))

	Controls	*Left ventricular hypertrophy*	*Left ventricular dilatation*
Ventricular systole			
Onset (ms)	80 (25)	100 (40)	140 (65)†
Excursion (cm)	1·0 (0·2)	0·8 (0·2)*	0·4 (0·2)†
Early diastole·			
Velocity (cm/s)	4 (1)	3·5 (1·7)	2·4 (1·0)†
Excursion (cm)	0·5 (0·1)	0·3 (0·1)†	0·3 (0·2)†
Atrial systole			
Excursion (cm) (%)	0·6 (0·2) (59 (13))	0·5 (0·2) (63 (21))	0·3 (0·2)† (44 (36)†)
Anteroposterior dimension:			
End ventricular systole (cm)	3·0 (0·5)	3·4 (0·6)	3·7 (1·0)
End ventricular diastole (cm)	2·2 (0·5)	2·9 (0·6)*	3·3 (0·6)*

*p < 0·05 and †p < 0·01 compared with controls.

Standard assessment of atrial systole (table 3).—The mitral flow velocity and the increase in the minor axis of the ventricle during atrial systole were 0·5 (0·1) m/s and 31 (17)% respectively. The relative amplitude of the apexcardiogram 'a' wave was 12 (6)%.

Left ventricular function (table 4).—Fractional shortening of the minor axis was 0·28 (0·04), septal thickness was 1·2 (0·2) cm, and posterior wall thickness was 1·1 (0·25) cm. In diastole the isovolumic relaxation time was 70 (20) ms and the peak rates of change in the minor axis dimension and posterior wall thinning were 8·4 (2·8) cm/s and 6·2 (1·6) cm/s respectively.

LEFT VENTRICULAR HYPERTROPHY

Atrioventricular ring movement.—The pattern of left atrioventricular ring motion was abnormal in patients with left ventricular hypertrophy. The extent and velocity of upward motion during early diastole were lower than normal (extent 0·5 (0·3) cm, velocity 7 (3) cm/s; both p < 0·01 *v* controls) and the distance moved during atrial systole was proportionately greater than normal (50 (12)%, p < 0·05). Despite these changes the timing, pattern, and extent of right sided ring motion remained normal. The proportions of ventricular inflow due to mitral ring movement as distinct from transmitral flow during early diastole and atrial systole were similar to normal (8 (2)% and 8 (4)% respectively) (table 5).

Anteroposterior left atrial dimension.—A reduced anteroposterior change during ventricular systole (0·8 (0·2) cm, p < 0·05 *v* controls) meant that the anteroposterior dimension was increased at ventricular end diastole (2·9 (0·6) cm, p < 0·05 *v* controls). Despite this, and despite reduced early diastolic movement (0·3 (0·1) cm, p < 0·05 *v* controls), atrial systolic motion remained normal. Anteroposterior changes were synchronous with mitral ring motion as they were in the controls.

Standard assessment of atrial systole.—The 'a' wave amplitude on the apexcardiogram and atrial systolic mitral flow velocity were increased (apexcardiogram 19 (11)%, p < 0·05 *v* normal; velocity 0·7 (0·2) m/s, p < 0·01 *v* controls (table 3)). The increase in the minor axis during atrial systole was normal (34 (17) %).

Table 3 Standard assessment of atrial systole (mean (1 SD))

	Controls	*Left ventricular hypertrophy*	*Left ventricular dilatation*
Minor axis increase (%)	31 (17)	34 (17)	21 (15)*
Apexcardiogram 'a' wave (%)	12 (6)	19 (11)*	31 (17)†
Mitral velocity (m/s)	0·5 (0·1)	0·7 (0·2)†	0·6 (0·3)

*$p < 0{\cdot}05$ and †$p < 0{\cdot}01$ compared with controls.

Table 5 Ratio of long axis change to transmitral distance (%)

	Controls	*Left ventricular hypertrophy*	*Left ventricular dilatation*
Early diastole	8·0 (2·1)	8·4 (1·9)	5·8 (3·0)
Atrial systole	9·8 (3·9)	8·2 (4·5)	3·0 (0·6)*

*$p < 0{\cdot}01$ compared with controls.

Left ventricular function.—Fractional shortening (0·33 (0·66)) was normal (table 4). Early diastole was, however, abnormal and was characterised by increased isovolumic relaxation time (90 (30) ms, $p < 0{\cdot}05$ *v* controls) and a reduced peak rate of posterior wall thinning (4·6 (1·8) cm/s, $p < 0{\cdot}01$ *v* controls).

DILATED CARDIOMYOPATHY

Atrioventricular ring movement.—Downward movement of the mitral and tricuspid rings during ventricular systole were both diminished (mitral 0·7 (0·2) cm, tricuspid 1·6 (0·6) cm; both $p < 0{\cdot}01$ *v* controls). The pattern of upward movement differed on the right and left sides. During early diastole upward mitral ring displacement was diminished (extent 0·4 (0·2) cm, $p < 0{\cdot}01$ *v* normal, velocity 5 (2) cm/s, $p < 0{\cdot}05$ *v* controls), whereas a normal extent of upward tricuspid motion was maintained due to a considerably increased velocity (11 (4) cm/s, $p < 0{\cdot}01$ *v* controls). Upward motion of both sides during atrial systole was reduced (mitral 0·3 (0·2) cm, tricuspid 0·4 (0·4) cm; both $p < 0{\cdot}01$ *v* controls). The proportion of upward movement of the mitral ring to transmitral flow was normal in early diastole (6 (3)%) but was reduced during atrial systole (3 (2), $p < 0{\cdot}01$ *v* controls).

Anteroposterior left atrial dimension.—Anteroposterior left atrial change during ventricular systole was reduced (0·4 (0·2) cm, $p < 0{\cdot}01$ *v* normal) and the end diastolic dimension was increased (3·3 (0·6) cm, $p < 0{\cdot}01$ *v* controls). The pattern of change during diastole was normal. Anteroposterior changes were again synchronous with changes in mitral ring position throughout the cardiac cycle.

Standard assessment of atrial systole.—Though the amplitude of the 'a' wave on the apexcardiogram was considerably raised (31 (17)%, $p < 0{\cdot}01$ *v* controls), the increase in the minor axis of the left ventricle during atrial systole was reduced (21 (15)%, $p < 0{\cdot}05$ *v* controls) and peak mitral flow velocity was normal (0·6 (0·3) m/s, p = NS).

Left ventricular function.—Fractional shortening (0·16 (0·05)) and septal thickness (1·0 (0·3) cm) were reduced ($p < 0{\cdot}05$ and $p < 0{\cdot}01$ *v* controls respectively). The isovolumic relaxation time was short (40 (30) ms, $p < 0{\cdot}01$ *v* controls), suggesting raised left atrial pressure, and the peak rate of wall thinning was low (3·6 (1·9) cm/s, $p < 0{\cdot}01$ *v* controls).

Table 4 Left ventricular function (mean (1 SD))

Variable	*Controls (n = 20)*	*Left ventricular hypertrophy (n = 28)*	*Left ventricular dilatation (n = 16)*
Fractional shortening	0·28 (0·04)	0·33 (0·06)	0·16 (0·05)†
Posterior wall thickness (cm)	1·1 (0·25)	1·7 (0·4)†	1·2 (0·2)
Septal thickness (cm)	1·2 (0·2)	2·5 (0·7)†	1·0 (0·3)*
Isovolumic relaxation time (ms)	70 (20)	90 (30)*	40 (30)†
Peak rate of dimension increase (cm/s)	8·4 (2·8)	7·6 (2·7)	6·7 (3·0)
Peak rate of posterior wall thinning (cm/s)	6·2 (1·6)	4·6 (1·8)†	3·6 (1·9)†
RR interval (ms)	850 (70)	910 (60)	780 (90)

*$p < 0{\cdot}05$ and †$p < 0{\cdot}01$ compared with controls.

Discussion

Though normal atrial function is well recognised as contributing significantly to ventricular filling, the way it does so has been little studied. We therefore adapted simple non-invasive methods based on ultrasound to see how changes in atrial and ventricular dimensions are related to those in transmitral flow velocity in healthy individuals and patients with ventricular disease.

Changes in left atrial volume can be assessed from the motion of the atrioventricular ring[9–11] and also from the anteroposterior diameter, itself reflected mainly in aortic root motion because the posterior aortic wall is fixed to the mediastinum.[12] These two measurements differ in that the atrioventricular ring is also in contact with ventricular myocardium while the left atrial diameter is not. The anteroposterior diameter thus reflects left atrial events alone,[13] whereas motion of the atrioventricular ring allows atrioventricular interactions to be studied.

In healthy individuals left atrial volume increases during ventricular systole because the mitral valve is closed and venous return continues. Two mechanisms can be identified. Pulmonary venous return derives ultimately from right ventricular systolic function. In addition to this, downward motion of the atrioventricular ring towards the apex of the ventricle, while an integral part of the normal contraction and ejection mechanisms of the ventricle,[10 14] also increases atrial volume and potentially facilitates the inflow of blood from the pulmonary veins.[8] Though this latter mechanism involves forces very much greater than those resulting from the venous return, we found no evidence that either of these very different mechanisms predominated in healthy individuals because there was no significant phase delay between downward motion of the mitral ring and the increase in the anteroposterior axis. In addition, the extent and peak velocities of changes in the two axes of the left atrium that we measured were similar. Thus the rate of inflow of blood into the left atrium exceeds the potential volume increase due to atrioventricular ring motion alone, so that changes in atrial dimensions caused by left ventricular contraction and pulmonary venous inflow seem to be matched in resting healthy individuals. During ventricular diastole changes in the anteroposterior diameter and mitral ring position were also closely matched in extent, velocity, and timing. When the heart rate is slow, as it was in our subjects, changes in atrial dimensions reflect the characteristic tripartite filling pattern of left ventricular inflow, with a rapid fall during early diastole and again during atrial systole after the intervening period of diastasis. During early diastole, the fall in anteroposterior axis is the simple effect of left ventricular filling. Upward motion of the mitral ring, however, occurs in the face of increasing blood flow velocity across the mitral valve. Such acceleration implies a positive pressure difference from atrium to ventricle, so that movement of the atrioventricular ring in the opposite direction must be the result of a greater force. This force was not due to myocardial contraction because it operated during the time when both atrium and ventricle were relaxed. Thus is was likely to have been an elastic force, dissipating energy stored in the atrial or the ventricular wall at the end of the previous ventricular systole. Dissipation of energy stored in the atrial wall would be of theoretical interest as a ventricular restoring force with an anatomical basis outside rather than within the ventricle, the left atrium acting as a modified reservoir of stored energy derived from the ventricular myocardium rather than the venous return.

During atrial systole the long and anteroposterior atrial axes shortened equally. We found no evidence of regional non-uniformity in the extent or timing of atrial systole, as are present with normal ventricular systole.[15] The increase in ventricular volume during atrial systole was brought about by two discrete mechanisms. It is usually assumed that the increase in ventricular volume during filling can be assessed from the product of the time integral of the transmitral flow velocity, usually detected by a Doppler transducer on the chest wall, and the effective mitral valve area.[16] Motion of the mitral ring may modify this simple assumption, however. Keith deduced from anatomical considerations that because the atrioventricular ring moves towards the left atrium, blood within the left atrium at the start of atrial systole is within the left ventricle at the end.[17] Because the blood itself does not move, no flow velocities can be detected by a transducer working from a fixed external reference point. Furthermore, this mechanism does not require the development of an atrioventricular pressure difference for its operation; and, unlike a simple increase in atrial pressure, it is directional, with no tendency for retrograde flow up the pulmonary veins. Since the effective mitral valve area for this mechanism was the same as for transmitral flow, we could estimate that upward motion of the mitral ring contributed approximately 10% of left ventricular filling during both early diastole and atrial systole in our normal group.

Events on the right side were in general similar to those on the left. As has been previously shown by angiography,[18] the right atrioventricular ring moves further than the left during ventricular systole, presumably reflecting the striking differences in right and left ventricular fibre architecture. Despite altered left sided motion in left ventricular hypertrophy, the right side continued to move normally. In the patients with dilated cardiomyopathy the increased rate of expansion of right ventricular long axis in early diastole, indicated in this study by an increased velocity of upward tricuspid ring motion, has been described as the mechanism underlying the generation of a right ventricular third sound in the presence of raised atrial pressure.[19 20]

Left atrial systole was significantly modified in disease. In patients with left ventricular hypertrophy, the apexcardiogram 'a' wave amplitude, reflecting pressure generated by the loaded atria,[21] and transmitral flow velocity were increased. Mitral ring motion and changes in atrial anteroposterior dimension remained synchronous as in the healthy controls. In early diastole, however, the amplitude of upward motion of the mitral ring was diminished; and it was correspondingly increased during atrial systole, when the anteroposterior axis reduced normally, suggesting that atrial systolic shortening of the long axis may have been preferentially accentuated. Thus the increase in the left ventricular long axis matched the increase in minor axis. This was not the case in patients with dilated cardiomyopathy. Though the total amplitude of atrioventricular ring motion was reduced, presumably because of impaired ventricular systolic shortening, the relative change with left atrial systole was further diminished as was the contribution of ring motion to overall atrial flow. At the same time the relative prominence of the 'a' wave on the apexcardiogram increased, showing that the ability of the atrium to develop pressure was unimpaired. This combination of an increased pressure 'a' wave and a reduced transmitral flow is compatible with low end diastolic ventricular compliance.[22]

As a result of these studies we can extend traditional views on atrial function, which have divided it into reservoir, conduit, and pump functions.[5-7] Reservoir function requires that the atrioventricular valves are closed, so that as atrial volume increases, pressure is determined passively by the compliance of the atria. Conduit function occurs when the valves are open and implies that the flow rate entering is equal to that leaving, so the volume of blood within the atria remains constant. It dissociates flow from volume changes in the atria and so cannot be detected from measurements of the pressure and volume or dimension of the atrium alone. Pump function represents work done on the circulating blood by the contracting atria. These functions do not take into account any interaction between the atria and adjacent structures, though such interactions clearly exist. Downward motion of the atrioventricular ring during ventricular contraction enlarges the atrial cavity in a manner quite unrelated to reservoir function, and the work done on the atria by this means may contribute to forward pulmonary venous flow. Then, in early diastole, atrial emptying by upward motion of the atrioventricular ring seems to be the result of elastic forces with their likely origin in ventricular systole. Upward motion of the atrioventricular ring during atrial systole may have the advantage of promoting an increase in the ventricular long axis in preference to pulmonary venous backflow, a mechanism that is lost in patients with reduced left ventricular compliance. These results indicate that, contrary to previous descriptions, the atria cannot be considered in isolation from the adjoining ventricles. For interpretation of measurements of atrial pressure and transmitral flow, these interrelations should be appreciated; this may lead to an improved understanding of how atrial mechanical behaviour could be altered to the advantage of patients with ventricular disease.

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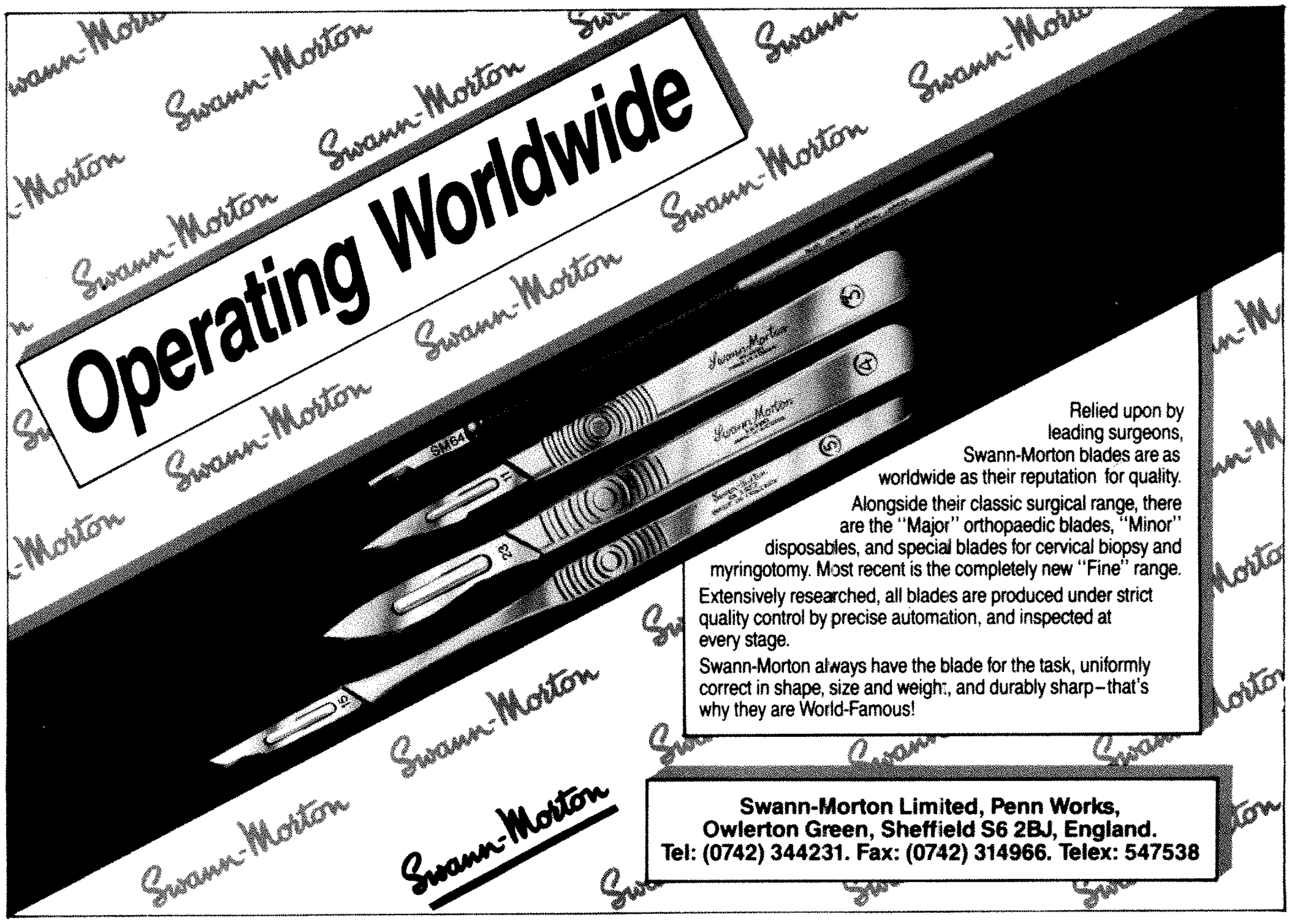

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Br Heart J 1991;65:37–40

End diastolic flow velocity just beneath the aortic isthmus assessed by pulsed Doppler echocardiography: a new predictor of the aortic regurgitant fraction

Christophe Tribouilloy, Pierre Avinée, Wei Feng Shen, Jean-Luc Rey, Michel Slama, Jean-Philippe Lesbre

Abstract

End diastolic flow velocity just beneath the aortic isthmus was measured within 72 hours of cardiac catheterisation by pulsed Doppler echocardiography in 30 controls and 61 patients with aortic regurgitation. The end diastolic flow velocity was determined at the peak R wave on a simultaneously recorded electrocardiogram. In all controls there was no reverse flow at the end diastole beneath the aortic isthmus. In patients with aortic regurgitation the end diastolic flow velocity correlated well with the angiographic grade of regurgitation ($r = 0{\cdot}81$) and regurgitant fraction ($r = 0{\cdot}82$). The mean (SD) values were 6·3 (5·2), 12·2 (4·3), 22·1 (5·7), and 34·3 (9·3) cm/s for patients with regurgitant fraction of <20%, between 20% and 40%, between 41% and 60%, and >60%, respectively. An end diastolic flow velocity of >18 cm/s predicted a regurgitant fraction of ⩾40% with a sensitivity of 88·5% and a specificity of 96%.

The study suggests that the pulsed Doppler derived end diastolic flow velocity is a useful index in the routine non-invasive assessment of the severity of aortic regurgitation.

With the widespread application of both pulsed and continuous wave Doppler echocardiography[1–3] and colour flow imaging,[4] several variables have been proposed as a measure of the severity of chronic aortic regurgitation. Clinical study showed pandiastolic flow in the descending aorta in patients with aortic regurgitation.[5] We found that it was easy to measure the end diastolic flow velocity just beneath the aortic isthmus by pulsed Doppler echocardiography and that this method provides semiquantitative information on the degree of aortic regurgitation.[6] In the present study we investigated further the usefulness of this measurement in estimating the aortic regurgitant fraction.

Patients and methods

PATIENTS

Seventy patients with chronic aortic regurgitation underwent cardiac catheterisation and Doppler echocardiography within 72 hours of each other. Nine patients with poor echogenicity were excluded (pure aortic regurgitation in four and associated aortic stenosis in five). We studied the remaining 61 patients (43 men and 18 women, mean (SD) age 60 (17) years (range 22–84)). All patients were in stable sinus rhythm and had no angiographically significant mitral regurgitation. Forty two patients had pure aortic regurgitation and 19 had associated aortic stenosis. The cause of aortic regurgitation was rheumatic fever in 22, degenerative abnormality in 29, infective endocarditis in eight, post-traumatic lesion in one, and prosthetic valve dysfunction in one. All patients had had a clinical diagnosis of aortic regurgitation for more than six months.

Thirty patients without valve disease served as a control group. Cardiac catheterisation and angiography were performed because of atypical chest pain. All patients had normal electrocardiograms, chest *x* ray, and Doppler findings.

DOPPLER ECHOCARDIOGRAPHIC EXAMINATION

We used an ATL Mark 600 or a Hewlett-Packard 77020 system equipped with a 3 or 2·5 MHz pulsed Doppler transducer respectively. Patients were placed in a supine position with the head overextended and the shoulders raised. The transducer was positioned in the suprasternal notch and directed downwards to bring the ultrasound beam on to the thoracic aorta at a point between its horizontal and descending portions. The sample volume was placed in the proximal descending aorta just beneath the aortic isthmus and the origin of the left subclavian artery. The Doppler beam was aligned in parallel with the axis of aortic blood flow by showing a maximal systolic (negative) flow velocity curve. Doppler filters were adjusted to minimal values, and gains were reduced to obtain a contrasted but uninterrupted display of the model Doppler frequencies. Patients with chronic aortic regurgitation often show reverse flow velocities throughout diastole in the descending aorta and the flow velocity is relatively constant after mid diastole.[7] The end diastolic flow velocity (cm/s) was measured at the peak of the R wave on a simultaneously recorded electrocardiogram (fig 1).

The reproducibility of this measurement using this method was tested in 20 patients with aortic regurgitation: the mean (SD) intra

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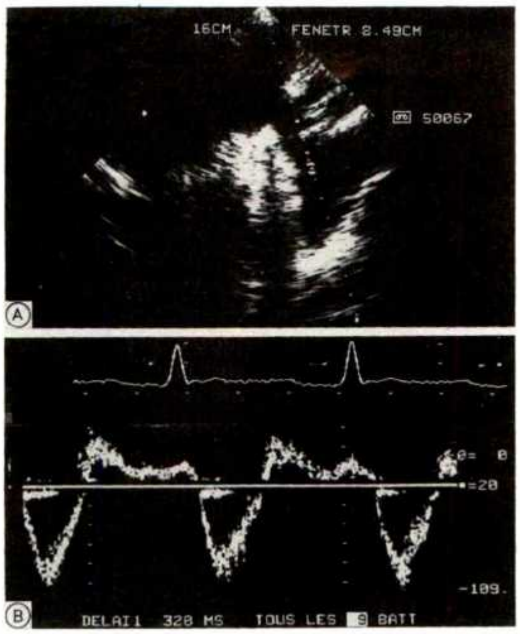

Figure 1 Measurement of end diastolic flow velocity by pulsed Doppler echocardiography. (A) Ultrasound beam aligned with the axis of the descending aorta with sample volume just beneath the aortic isthmus and junction with subclavian artery. (B) Flow velocity curve. Systolic flow velocity appears below the O line and diastolic flow velocity above it. The end diastolic flow velocity was measured at the peak of the R wave on a simultaneously recorded electrocardiogram.

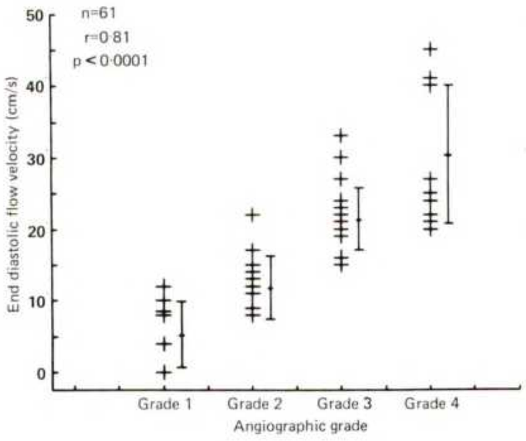

Figure 2 Correlation between end diastolic flow velocity measured by pulsed Doppler method and angiographic grade of aortic regurgitation. Mean and standard deviations are shown for each angiographic grade. Some points represent more than one patient.

and inter observer variabilities were 4·4 (3·2)% and 5·6 (3·6)% respectively.

CARDIAC CATHETERISATION

Right and left heart catheterisations were performed within 72 hours of the Doppler echocardiographic studies. Cardiac output was determined by the thermodilution technique and total left ventricular output was measured from left ventriculography performed in the 30° right anterior oblique projection. Regurgitant fraction was calculated by the standard formula. Aortography was performed in 30° right anterior oblique projection with 40–60 ml of contrast media injected through a 7F pigtail catheter positioned 2–3 cm above the aortic valve. The degree of aortic regurgitation was graded on a scale of I to IV by the method of Sellers *et al.*[8]

Table 1 Pulsed Doppler prediction of angiographic grade of aortic regurgitation by end diastolic flow velocity. The pulsed Doppler class accorded with the angiographic class in 39 of 61 patients and no patient was misclassified by more than one class

	Doppler end diastolic flow velocity (cm/s)			
Angiographic grade	*0–9*	*>9–18*	*>18–30*	*>30*
I	5	3	0	0
II	3	13	2	0
III	0	4	16	2
IV	0	0	8	5

STATISTICAL ANALYSIS

The results were expressed as mean (1 SD). We tested the relation between the end diastolic flow velocity and angiographic grades of regurgitation by the Spearman correlation analysis; for continuous data we used linear regression analysis.

Results

CONTROL GROUP

In all 30 controls the mean (1 SD) value of peak systolic flow velocity was 1·10 (0·20) m/s. Early diastolic flow beneath the aortic isthmus was detected with a velocity of <0·25 m/s and lasting <200 ms. There was no reverse flow during mid and late diastole.

AORTIC REGURGITATION

In 61 patients there was a good correlation between end diastolic flow velocity and the angiographic grade of aortic regurgitation (fig 2).

Mean (SD) end diastolic flow velocity in eight patients with grade I regurgitation was 5·3 (4·6) cm/s (end diastolic flow velocity was zero in four), for 18 patients with grade II regurgitation it was 11·8 (4·4) cm/s, for 22 patients with grade III regurgitation it was 21·4 (4·3) cm/s, and for 13 patients with grade IV regurgitation it was 30·4 (9·6) cm/s. Though there was some overlap in end diastolic flow velocity among individuals with each of the four grades of aortic regurgitation, this measurement was a good indication of the severity of aortic regurgitation. Thirty one of 35 patients with end diastolic flow velocity >18 cm/s had grade III or IV regurgitation, whereas 24 of 26 patients with end diastolic flow velocity <18 cm/s had grade I or II. Therefore, an end diastolic flow velocity >18 cm/s predicted severe aortic regurgitation (⩾ grade III) with a sensitivity of 88·5% and a specificity of 92·3% (table 1).

The end diastolic flow velocity correlated

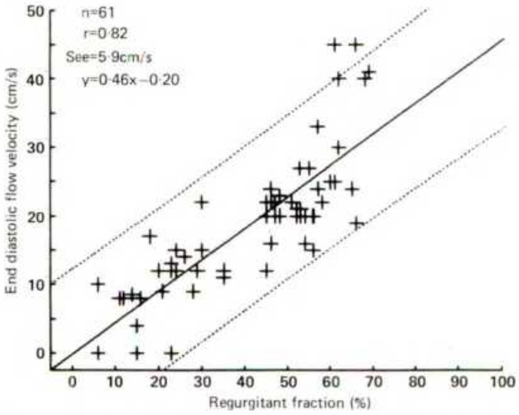

Figure 3 Correlation between end diastolic flow velocity measured by pulsed Doppler method and regurgitant fraction by haemodynamic method. Broken lines show 95% confidence interval and solid line is the regression line. Some points represent more than one patient.

Table 2 Pulsed Doppler prediction of angiographic regurgitant fraction by end diastolic flow velocity. The pulsed Doppler class accorded with the angiographic class in 46 of 61 patients and no patient was misclassified by more than one class

	Doppler end diastolic flow velocity (cm/s)			
Regurgitant fraction (%)	*0–9*	*>9–18*	*>18–30*	*>30*
0–20	7	3	0	0
21–40	1	14	1	0
41–60	0	4	20	2
>60	0	0	4	5

well with the regurgitant fraction measured by a combined haemodynamic and angiographic method (fig 3). Mean (SD) end diastolic flow velocity was 6·3 (5·2) cm/s in 10 patients with a regurgitant fraction <20%, 12·2 (4·3) cm/s in 16 patients with a regurgitant fraction between 20–40%, 22·1 (5·7) cm/s in 26 patients with a regurgitant fraction between 41–60%, and 34·3 (9·3) cm/s in nine patients with a regurgitant fraction >60%. The end diastolic flow velocity reliably classified the regurgitant fraction. Thirty one of 35 patients with end diastolic flow velocity >18 cm/s had a regurgitant fraction >40%. In contrast, 25 of 26 patients with end diastolic flow velocity <18 cm/s had a regurgitant fraction of <40%.Therefore, an end diastolic flow velocity of >18 cm/s identified patients with regurgitant fraction >40% with a sensitivity of 88·5% and a specificity of 96% (table 2).

Discussion

An excellent alignment can be achieved between the ultrasound beam and blood flow during Doppler assessment of flow velocity in the descending aorta and the flow velocity at the end of diastole measured just beneath the aortic isthmus is a good indicator of the severity of aortic regurgitation.

Previous studies of the flow profiles in the aorta showed an irregular flow velocity pattern in the ascending aorta with moderate or severe regurgitation.[10] Because flow velocity across the lumen varies in diastole calculation of forward or reverse flow is unreliable. In contrast, flow in the descending aorta produces a much flatter velocity profile.[9–11] In most of our patients we found a narrow band of frequencies even when regurgitation was severe. Furthermore, movement during the cardiac cycle is much less in the aortic isthmus than the ascending aorta,[11] allowing better positioning of the sample volume. In our controls the early diastolic reverse flow detected in the descending aorta by the Doppler method may reflect compliance of the aortic wall, and it may be impossible to define a shape that takes account of the alteration in compliance and the diastolic reflux caused by aortic regurgitation.[10] For these reasons, flow velocity during late diastole in the descending aorta has been investigated extensively to assess the severity of aortic regurgitation.

Boughner used continuous Doppler echocardiography to measure the flow velocity in the descending aorta; he found that the ratio between the diastolic and systolic flow velocity-time integrals allowed measurement of aortic regurgitant fraction.[5] Touche *et al* proposed a modified method using pulsed Doppler in which the flow velocity-time integral ratio was multiplied by the ratio of aortic diastolic area to systolic area obtained from an M mode echocardiogram.[11] They also reported a good correlation between this measurement and regurgitant fraction determined invasively. Diebold *et al* also reported that the ratio of the end diastolic to the peak systolic velocity can also be obtained from pulsed Doppler echocardiography and that it gives semiquantitative information about the severity of aortic regurgitation.[10] Pulsed Doppler is better than continuous wave Doppler because it is not affected by the venous flow velocities during diastole because the site of the sample volume can be accurately located. These three methods of measuring the regurgitant fraction depend largely on determinations of systolic flow velocity. Thus they may not be reliable in the presence of associated aortic stenosis.[10]

A preliminary study from our laboratory showed that a simple measure of the end diastolic flow velocity gave an accurate semiquantitative measure of the severity of aortic regurgitation, and it can be easily determined in most patients with aortic regurgitation.[6] The results of this study confirm our previous observations and further indicate the high sensitivity and specificity of an end diastolic flow velocity of >18 cm/s in predicting moderate to severe (grade ⩾III) aortic regurgitation and identified patients with a regurgitant fraction of >40%. This suggests that the end diastolic flow velocity may also be used to predict the aortic regurgitant fraction.

There are several potential limitations of this method. If aortic regurgitation is slight, velocities in the reverse flow will be low and may not be recorded if a filter with too high a cut off frequency is used. In patients with a ductus arteriosus, aortopulmonary fistula, aortic coarctation at the isthmus level, or aortic dissection, this method is not feasible because of a continuous flow component in these regions.[11] Because the accuracy of end diastolic flow velocity in measuring the severity of aortic regurgitation relies on a relatively constant reverse flow velocity throughout diastole, the regurgitant fraction may be overestimated during tachycardia (>120 beats/min) and underestimated during bradycardia (<50 beats/min).[12] In atrial fibrillation, when the diastole is prolonged, there may be no end diastolic flow. The compliance of the left ventricle in acute aortic regurgitation might well be quite different from that of patients with chronic aortic regurgitation. There may be equilibration of aortic and ventricular pressures before end diastole, which may lead to cessation of reverse flow before the proposed measurement.

The end diastolic flow velocity just beneath the aortic isthmus can be measured easily in most patients with chronic aortic regurgitation and is an accurate indicator of the regurgitant fraction. It may be useful in the routine assessment of patients with chronic aortic regurgitation. The effect of various afterloads on this relation should be investigated.

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Interatrial shunt flow profiles in newborn infants: a colour flow and pulsed Doppler echocardiographic study

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Abstract

Interatrial shunt flow profiles in 36 normal term infants were examined serially by colour flow and pulsed Doppler echocardiographic techniques from within an hour of birth to four or five days after birth. Shunt flow across the foramen ovale was detected in 33 normal infants (92%) within an hour of birth (mean 40 minutes). The occurrence of interatrial shunting decreased with age, but a shunt signal was still detected in 17 infants (47%) on the fourth or fifth day of life, by then the ductus arteriosus had already closed in all the normal infants. The direction of interatrial shunt flow was predominantly left-to-right, but in 64% there was a coexistent small right-to-left shunt in diastole within an hour of birth; by four to five days it was found in 19%. In the six patients with persistent fetal circulation the direction of the interatrial shunt flow was predominantly right-to-left with biphasic peaks in diastole and systole at the early stage of the disease, and the period of right-to-left shunt flow during each cardiac cycle was significantly longer than that in normal infants examined within 1 hour of birth. In all patients the ductus closed before the foramen ovale. At the time of ductal closure in all patients with persistent fetal circulation right-to-left shunt flow was seen during diastole and its period was still prolonged.

These findings suggest that interatrial shunting, predominantly left-to-right, is common in normal newborn infants. Evaluation of the characteristics of the interatrial shunt by Doppler echocardiography may be useful for predicting the progress of or improvement in neonates with persistent fetal circulation.

Dramatic changes occur in the circulation of the newborn infant. In most normal newborn infants the foramen ovale functionally closes within an hour of birth as a result of the increase in pulmonary venous return, decrease in blood flow in the inferior vena cava, and increase in systemic arterial resistance after delivery.[1,2] However, a recent Doppler echocardiographic study suggested that in normal neonates, right-to-left shunting occurred during most of diastole, with coexistent left-to-right shunting for some time.[3] In addition, little is known about the prevalence and serial changes in interatrial shunt flow in normal infants because previous studies did not directly analyse interatrial blood flow.[3-5] Also interatrial haemodynamic function in patients with persistent fetal circulation syndrome is poorly understood.

Therefore, we analysed interatrial shunt flow profiles using colour flow and pulsed Doppler echocardiography to establish (*a*) the frequency of a patent foramen ovale during normal postnatal life, (*b*) flow dynamics across the foramen ovale in normal infants and in patients with persistent fetal circulation, and (*c*) the relation between ductal shunting or closure and interatrial shunt flow profiles.

Subjects and methods

SUBJECTS

We studied 36 term infants with a gestational age of >38 weeks. Each was the product of a normal pregnancy, labour, and delivery. Infants were of average size for gestational age, and birth weight ranged from 2600 to 3700 g (mean 3100 g). None had received any medication or supplementary oxygen before the study. All infants had normal findings on physical examination and echocardiographic examination showed that they were free of cardiovascular disease. The initial study was performed within an hour of birth (mean 40 minutes) in all infants and serial studies were performed during the first five days after birth at 3 (0·5) (mean (SD)), 24 (1), and 109 (8) hours (4 to 5 days). These examinations were undertaken when the infants were in a quiet state.

We also studied six term infants with typical persistent fetal circulation and who presented with early cyanosis within 12 hours of birth, with low arterial oxygen tension (under 45 mm Hg when inhaling 100% oxygen) after structural heart disease had been excluded by cross sectional and Doppler echocardiography.[6] Birth weights ranged from 2400 to 3400 g (mean 2900 g). There was no recognisable pulmonary, haematological, or central nervous system disease in five patients but one had mild pulmonary parenchymal disease caused by meconium aspiration. Initial examinations were performed within 24 hours of birth in all patients and serial studies were performed one or two times a day until all clinical findings disappeared.

COLOUR FLOW AND DOPPLER ECHOCARDIOGRAPHIC EXAMINATIONS

All infants were studied with a commercially available system (Hewlett-Packard, Model 77020 AC) with a 5 MHz shallow focus or 3·5 MHz transducer. For analysis we used the image that best demonstrated the colour flow imaging of transatrial flow. This was most often obtained from the subxiphoid approach as described previously.[4] The lower parasternal approach was also attempted in some infants. In addition, the entire length of the ductus arteriosus was visualised from the high parasternal approach.[7] For Doppler colour flow imaging, flow directed toward the transducer was conventionally coded as red whereas flow directed away from the transducer was blue. Variations in velocity were represented by the brightness and intensity of the colour. For colour flow imaging the gain was initially reduced and then progressively increased until an acceptable colour image was obtained. Interatrial left-to-right shunting was judged to be present when red, yellow, or mosaic signals crossed the atrial septum and extended into the right atrium. Right-to-left shunting was considered to be present if blue or mosaic signals crossed the atrial septum and extended into the left atrium. Ductal left-to-right shunting was considered to be present if red, yellow, or mosaic signals were seen across the ductus from the descending aorta to the main pulmonary artery. Right-to-left ductal shunting was judged to be present if blue or mosaic signals crossed the ductus from the main pulmonary artery to the descending aorta.

When colour mapping showed interatrial or ductal shunting the findings were confirmed by pulsed Doppler analysis, which indicated the direction of the flow across these orifices. The sample volume was placed on the colour Doppler echocardiographic shunt flow signal. Doppler profiles and simultaneous electrocardiograms were recorded at 50–100 mm/s and were stored on video tape for later playback and analysis in stop frame mode. When there was a bi-directional pattern at the site of the interatrial communication the time intervals were measured as described elsewhere.[8] In brief, the turning point from the right-to-left to the left-to-right shunt was designated as T_1 and the turning point from the left-to-right to the right-to-left shunt as T_2 (fig 1). The ratio of the T_1-T_2 interval to the RR interval of the electrocardiogram (T_1-T_2/RR) was calculated and a mean taken from the recordings of 10 consecutive beats.

STATISTICAL ANALYSIS

We used non-parametric techniques to analyse serial changes in the frequency of interatrial shunting and Student's t test for differences in mean values between the two groups. A probability value of <0.05 was regarded as significant.

Results

NORMAL NEWBORN INFANTS

Within an hour of birth left-to-right shunt flow was detected in 10 infants (28%) and bi-directional shunt flow in 23 (64%) (table, fig 2). The proportion in whom the foramen ovale was functionally closed did not change within three hours of birth but increased significantly from three to 24 hours ($p < 0.01$). There had been a further increase in the functional closure by the fourth and fifth days of life, but 10 (28%) infants still had a left-to-right shunt signal and seven (19%) a bi-directional one. The ductus arteriosus was patent three hours after birth in all infants and it closed functionally in 52% at 24 hours of life. By the fourth to the fifth day of life, there had been spontaneous functional closure of the ductus in all infants.

ANALYSIS OF INTERATRIAL SHUNT FLOW DYNAMICS IN HEALTHY NEWBORN INFANTS

A left-to-right shunt signal was recorded in systole and early diastole (fig 2). A slight right-to-left shunt signal was noted in diastole, mostly in atrial systole; during three examinations in two infants a right-to-left shunt signal was noted in both diastole and systole. In 23 infants with a bi-directional shunt flow within an hour of birth the mean T_1-T_2/RR ratio ranged from 0·68 to 0·95 (mean 0·85) (fig 3).

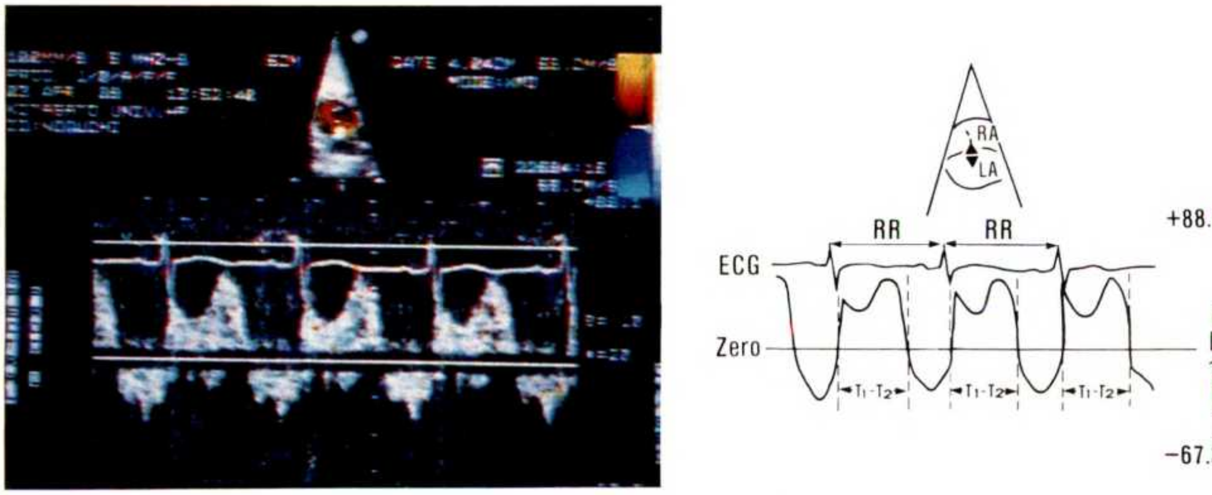

Figure 1 Interatrial shunt flow profile determined by Doppler echocardiography. The sample volume was placed at the site of the foramen ovale. Doppler spectral display above the zero line represents left-to-right flow and that below the zero line right-to-left. The duration of left-to-right interatrial flow (T_1-T_2) was measured and expressed as the ratio to the RR interval of the electrocardiogram (T_1-T_2/RR). ECG, electrocardiogram; LA, left atrium; RA, right atrium.

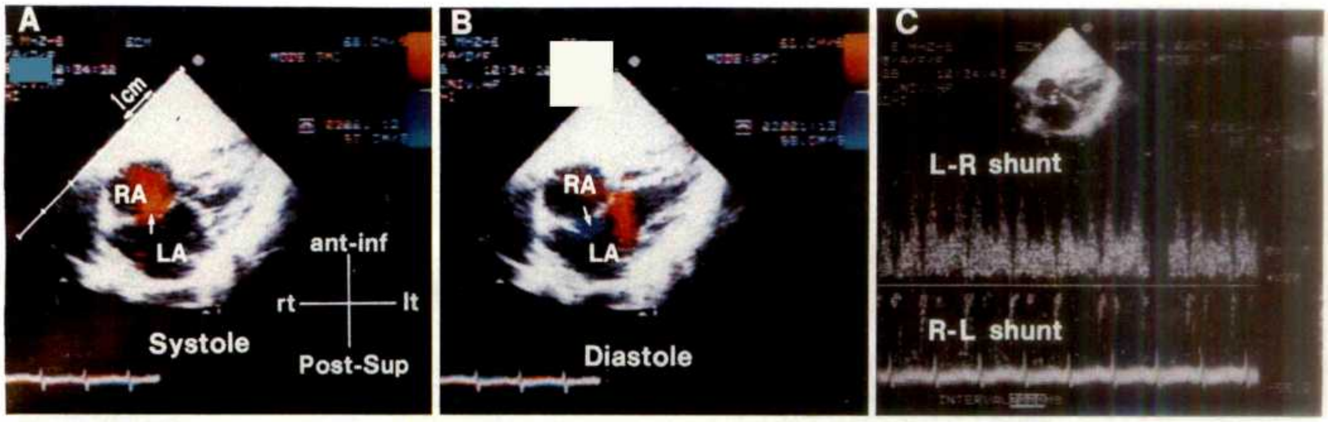

Figure 2 Colour flow and pulsed Doppler echocardiograms from a normal infant 30 minutes after delivery. (A) Subxiphoid view showing transatrial red signal (arrow) during systole, which is indicative of left-to-right shunt flow. (B) Note the blue signal (arrow) crossing from right atrium to left atrium in diastole. (C) Doppler signal showing that the direction of shunt flow is predominantly left-to-right (L–R), which is represented as Doppler signal toward the transducer. There was a small amount of right-to-left (R–L) shunt flow (Doppler signal away from transducer) of short duration in atrial systole. RA, right atrium; LA, left atrium; ant-inf, anterior-inferior; post-sup, posterior-superior; rt, right; lt, left.

Occurrence and direction of interatrial shunt flow

	Age after birth			
Direction of shunt flow	*20–60 (min) (n(%))*	*2–4 (h) (n(%))*	*23–26 (h) (n(%))*	*4–5 (days) (n(%))*
No shunt	3 (8)	4 (11)	13 (36)	19 (53)
Left-to-right shunt	10 (28)	13 (36)	12 (33)	10 (28)
Bi-directional shunt	23 (64)	19 (53)	11 (31)	7 (19)

PATIENTS WITH PERSISTENT FETAL CIRCULATION

At the initial examination the direction of interatrial shunt flow was predominantly right-to-left. The right-to-left shunt signal was recorded in both diastole and systole (fig 4). In two patients, small left-to-right shunt flow was detected in late systole. During the same period, the direction of the shunt flow within the ductus was predominantly right-to-left during systole and a small left-to-right shunt flow was detected during diastole in five patients. In all infants the ductus closed spontaneously between 24 hours and 120 hours after birth. At the time of ductal closure, interatrial shunt flow pattern was bi-directional and right-to-left shunt flow was detected in diastole in all six patients. Inspired oxygen was needed to maintain arterial oxygen tension between 50 and 60 mm Hg and the fraction of inspired oxygen ranged from 0·4 to 0·8 in each patient. Figure 3 shows that the $T_1 - T_2/RR$ ratio was significantly lower in the early phase of persistent fetal circulation than at the time of the ductal closure ($p < 0·01$) and both values were also significantly lower than those seen within an hour of birth in normal infants ($p < 0·01$). These bi-directional shunt patterns changed to left-to-right flow between the sixth and 20th day of life, and functional closure of the foramen ovale was noted in four patients by one month.

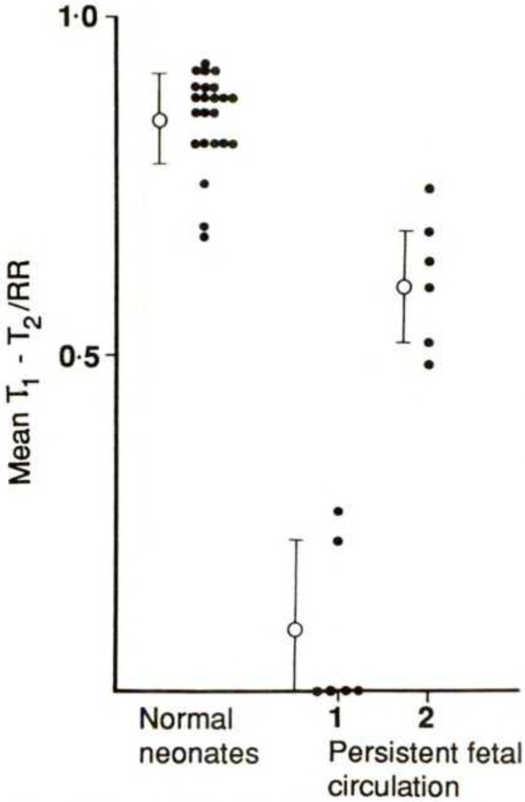

Figure 3 $T_1 - T_2/RR$ ratio in 23 normal infants with a bi-directional shunt flow and six patients with persistent fetal circulation (PFC) associated with considerable hypoxaemia (PFC-1) and ductal closure (PFC-2). The ratio of $T_1 - T_2/RR$ was smaller in PFC-1 than in normal infants ($p < 0·01$) and the value in the PFC-2 lay between values in the other two groups. The bars show mean (1SD).

Discussion

The data presented in this study showed that an interatrial shunt, predominantly left-to-right, was common in normal newborn infants. Colour flow mapping clearly distinguished between interatrial left-to-right shunting and flow in the superior vena cava. The results of colour flow mapping were confirmed by pulsed Doppler spectral analysis. The frequency of interatrial shunting did not change within the first three hours of birth, but it was significantly decreased from three to 24 hours after birth.

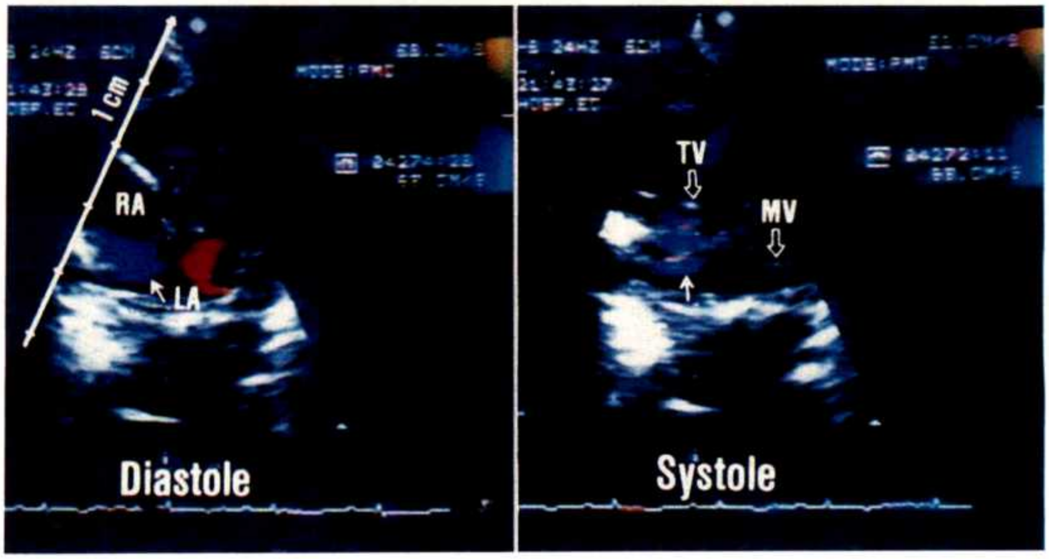

Figure 4 Colour Doppler echocardiograms from a patient with persistent fetal circulation. The transatrial blue signal, which is indicative of right-to-left shunt flow, was recorded in diastole. Note the mosaic signal (arrow) crossing to the foramen ovale in systole, indicating aliaising. Combined pulsed Doppler flow mapping and continuous Doppler technique showed that the blue signal originated from tricuspid regurgitant jet with high velocity of 3·5 m/s. TV, tricuspid valve; MV, mitral valve; RA, right atrium; LA, left atrium.

Drayton and Skidmore reported that ductal left-to-right shunt flow of 62 ml/kg/minute in term infants (95% confidence interval 43 to 82) shortly after birth decreased rapidly over the first 12 hours.[9] This result was consistent with the time course of changes in the morphology and flow patterns in the ductus arteriosus.[10 11] From these observations, it seems that the ductal left-to-right shunting in early postnatal life increases the frequency and magnitude of the left-to-right shunting through the foramen ovale. However, this mechanism does not explain the finding that interatrial shunt flow was detected in 47% of our subjects in the fourth to fifth day of life when the ductus had already closed in all infants. An earlier study[4] and our study found that the patent foramen ovale was either a redundant flap valve of the septum primum or a septal drop out at the superior rim of the septum primum. Others also found that patent foramina ovale were of normal size with unduly short or lax valves or were oversized with a normal sized valve.[12] Incompetence of the foramen ovale could occur if the development of various portions of the atrial septum was unbalanced, even in the absence of left atrial enlargement,[13] left sided lesions, and left ventricular failure.[14]

We assessed the phase and the duration of interatrial left-to-right or right-to-left shunting during each cardiac cycle from simultaneous recordings of the Doppler determined flow velocity pattern and the electrocardiogram. In most normal infants left-to-right shunting was dominant and slight right-to-left shunt flow was frequently noted in diastole; however, right-to-left shunt was seen in both diastole and systole in two infants with moderate tricuspid regurgitation. On the other hand, in all six patients with persistent fetal circulation, right-to-left shunting was dominant with biphasic peaks in diastole and in systole; but in two infants there was a small left-to-right shunt flow in later systole. We did not monitor respiration, and respiration especially mechanical ventilation, might have an effect on the interatrial shunt flow pattern. All six infants with persistent fetal circulation, however, showed conversion from dominant right-to-left shunting to bi-directional shunting during intubation and ventilation, and two had pure left-to-right shunting immediately before the extubation. These manoeuvres seemed to have little effect upon changes in the flow patterns in our patients.

The interatrial pressure gradient, which can determine the direction and the phase of shunt flow[5 15] may be affected by (*a*) the difference in distensibility of the right and left ventricles, (*b*) the capacitance of the systemic and pulmonary venous systems, (*c*) tricuspid regurgitation, and/or (*d*) persistence of a right-to-left or left-to-right shunt at the level of the ductus arteriosus. Analysis of the filling patterns of the right and left ventricles in normal neonates[3 16] suggested that the right ventricle becomes less distensible in the neonatal period and that this may cause diastolic interatrial shunting. If this is an effect of raised pulmonary resistance, then the pulmonary artery hypertension associated with persistent fetal circulation should predispose to an increase in diastolic right-to-left interatrial shunt flow as seen in our study. On the other hand, in an earlier cineangiographic study of ventricular volume in 10 patients with persistent fetal circulation we found that a decrease in pulmonary blood flow reduced the preload of the left ventricle.[17] We also found that a regurgitant tricuspid jet crossed the foramen ovale and entered the left atrium in two normal infants and four with persistent fetal circulation. These observations raise the possibility that systolic right-to-left shunting results from a smaller capacity of the pulmonary venous system than that of systemic venous system, from tricuspid regurgitation, or from both.

All six patients with persistent fetal circulation responded to conventional treatments such as infusion of tolazoline hydrochloride and hyperventilation. The ductus arteriosus closed before the foramen ovale in all six patients. At the time of the ductal closure the interatrial shunt flow pattern was bi-directional and the duration of diastolic right-to-left shunt flow was still longer than in normal infants. At this stage these patients had mild to moderate hypoxaemia. Our data indicate that relatively reduced distensibility of the right ventricle may persist after ductal closure, resulting in interatrial right-to-left shunting in diastole. The reduced distensibility of the right ventricle may be related to the persistence of relatively high pulmonary arterial pressure seen even after ductal closure in infants with persistant fetal circulation.[18]

Evaluation of interatrial shunting by Doppler echocardiography depends on this knowledge of the characteristics of interatrial shunting in normal newborn infants. The Doppler technique can be useful in assessing the severity and course of persistent fetal circulation.

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Flecainide in the treatment of fetal tachycardias

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Abstract

Fourteen mothers were treated with flecainide for fetal atrial tachycardias associated with intrauterine cardiac failure. Twelve of the 14 fetuses responded by conversion to sinus rhythm. One of the 12 fetuses subsequently died in utero. The remaining fetuses suffered no morbidity and were alive and well 3 months to 2 years after delivery. The two fetuses in whom atrial tachycardia did not convert with flecainide were successfully treated with digoxin. These results compare favourably with previous forms of antiarrhythmic treatment. After recent reports of the side effects of flecainide treatment, however, it has been advised that this drug should be confined to high risk patients and those with life threatening arrhythmias. The use of flecainide for fetal arrhythmias should be limited to patients with severe fetal hydrops and supraventricular tachycardias. It should not be the first drug of choice in atrial flutter.

Flecainide is a potent class 1c antiarrhythmic drug that is available in the treatment of atrial, junctional, and ventricular arrhythmias.[1] It acts on the fast sodium channel and slows conduction throughout the conduction system; its greatest effect is on the His bundle. It was effective and apparently safe in babies and children.[2] It was also successful for tachycardia in a fetus.[3] However, recent reports of an increase in the incidence of sudden death in adults with ventricular extrasystoles on maintainance flecainide treatment after myocardial infarction have led to recommendations that its use is restricted to patients with life threatening arrhythmias.[4,5] The intrauterine development of a fetal tachycardia and heart failure is certainly a life threatening condition; fetal mortality is reported to be 20–50%.[5–8] The variety of drugs reported to be useful in the treatment of fetal tachycardias—for example, digoxin, verapamil, quinidine, procainamide, amiodarone, and propranolol—gives some indication of the difficulty of managing these cases successfully.[6,9,10] We used flecainide in a group of 14 patients with fetal tachycardia. We present our results and recommendations for the use of this drug in this condition in the light of increasing concern about its safety.

Patients and methods

Fourteen patients presenting consecutively over a two year period with a fetal tachycardia and cardiac failure were treated with flecainide (an oral dose of 300 mg per day given to the mother). The table summarises the data on these patients. In all except patient 14, gross fetal hydrops was evident at presentation. The gestational age ranged from 23 to 36 weeks (mean 31). The rhythm disturbance was atrial flutter in two and supraventricular tachycardia in 12. One fetus had evidence of reduced left ventricular function on cross sectional, M mode, and Doppler evaluation. Congenital heart disease did not underlie the arrhythmia in any patient.

All patients were treated in hospital. Maternal serum concentrations of flecainide were monitored regularly and maternal electrocardiograms recorded weekly. Maternal serum concentrations of 400–800 $\mu g/l$ of flecainide

Summary of the clinical details and outcome in 14 fetuses treated with flecainide

Case No	Gestation at Presentation	Gestation at Delivery	Rhythm	Time to conversion	Duration of treatment	Drainage procedure	Hydrops at delivery	Outcome
1	32	37 +	AF	< 48 h	1 week	+	Mild	A and W
2	33	36	SVT	< 5 days	3 weeks	+	Mild	A and W
3	31	31 +	SVT	< 2 days	3 days	–	Mod	A and W
4	30	32 +	SVT	< 5 days	2 weeks	+	Mod	Cot death, at 4/12
5	23	23	SVT	< 24 h	3 days	–	Mod	IU death
6	36	37	SVT	< 24 h	1 week	–	Mild	A and W
7	28	39	SVT	< 48 h	5 weeks, F stopped, no recurrence	+	None	A and W
8	35	35 +	SVT	< 24 h	3 days	–	Mod	A and W
9	32	33 +	SVT	< 24 h	3 days, F stopped, reverted, F converted again	–	Mod	A and W
10	32	38	SVT	< 48 h	3 days, F stopped, reverted, F 1 week, stopped	+	None	A and W
11	23	38	SVT	< 48 h	3 days	–	None	A and W
12	33	37 +	SVT	< 4 days	4 days, F stopped, reverted, F till delivery	+	Mild	A and W
13	33	39	SVT	–	2 weeks, changed to D, converted	–	None	A and W
14	34	38	AF	–	2 days, changed to D, rate control	–	None	A and W

SVT, supraventricular tachycardia; AF, atrial flutter; A and W, alive and well; IU, intrauterine; D, digoxin; F, flecainide.

were maintained; two patients required 400 mg a day to achieve this. Maternal serum and cord concentrations of flecainide were measured at cordocentesis and delivery.

Results

The table shows the clinical details and results of treatment in 14 patients. In one patient (case 14) treatment with flecainide was stopped after 2 days because the fetus was found to be in atrial flutter and there was only mild fetal heart failure. In another patient (case 13) treatment was changed to digoxin after 2 weeks because only intermittent rate control had been achieved with flecainide. The remaining 12 fetuses converted to sinus rhythm in less than 5 days, most within 48 hours. In four of the 12 flecainide was stopped after conversion. In patient 7 flecainide was stopped at 33 weeks' gestation, 5 weeks after the start of treatment, and the arrhythmia did not recur. In patient 9 flecainide was stopped 2 days after conversion. Sinus rhythm was maintained for 3 days before the supraventricular tachycardia recurred. A second course of flecainide restored sinus rhythm. Patient 10 required two courses of flecainide but the drug was stopped at 34 weeks' gestation and the rhythm disturbance did not recur. In patient 12, an initial short course of flecainide controlled the tachycardia but the arrhythmia recurred. This mother was then maintained on flecainide treatment until delivery close to term.

Of the 12 patients who were successfully converted, there was one spontaneous intrauterine death. This occurred 3 days after treatment with flecainide was started. The fetus had converted to sinus rhythm and died within 24 hours of cordocentesis. All the remaining patients showed some resolution of hydrops at delivery; the most complete was in those fetuses remaining longer in utero after conversion of cardiac rhythm. Two patients had peritoneal drainage 2 weeks after conversion; one had a peritoneal shunt positioned before conversion; in neither did fluid reaccumulate. In two patients, drainage was performed less than a week after conversion but the ascites reaccumulated though it did improve or resolve with time. In one fetus the abdomen was drained just before delivery. All the patients (nine of the surviving 11) who delivered at less than 38 weeks' gestation were spontaneous deliveries except for patient 4 who required elective delivery at 32+ weeks because of severe pre-eclampsia.

Comparison of cord and maternal serum concentrations of flecainide indicated placental transfer of approximately 80% of the drug and showed that all fetuses had concentrations within the therapeutic range (400–800 μg/l).

Six of the 11 infants who were successfully treated with flecainide before birth and were born alive had recurrence of tachycardia postnatally. Five were treated with digoxin alone during the first year of life. One neonate required propranolol in addition to digoxin. In this last patient compromised left ventricular function recovered over the first 4 months of life. Five neonates required no treatment. The infant who suffered a cot death at four months old was not taking any treatment.

Discussion

Outcome in this group of patients compares favourably with our earlier results in a study of fetal atrial tachycardias.[11] In our previous series of 12 hydropic fetuses treated with digoxin and verapamil there were two deaths and a high rate of postnatal complications in the remaining 10. Control of the arrhythmia was achieved in seven of 12 compared with 12 of 14 in the present study but the main difference was in the speed of conversion—the mean time to conversion in the former group being 2–3 weeks compared with 48 hours in the flecainide group. Though the mean age at delivery was similar (35 weeks) in the digoxin and verapamil series and in the flecainide series, the main causes of morbidity in our earlier series were related to the complications of prematurity, especially ischaemic bowel disease. Quick control of the rhythm and time for some resolution of the hydrops will result in an infant in better condition at delivery and may even delay the onset of premature labour. It is possible that our current management procedures, such as peritoneal drainage, also contributed to the improved morbidity. Immediate resuscitation of the newborn is easier if tense ascites has been drained—even if just before delivery. Resolution of hydrops prenatally takes 1–2 weeks after rhythm control even with drainage procedures but the more complete it is before birth the less hazardous will be the postnatal course.

The ability to achieve therapeutic drug concentrations in the fetus quickly and the high rate of responsiveness make flecainide an attractive alternative to other drugs that are less well transferred by the placenta. The speed of achieving conversion allows the drug to be stopped after rhythm control as it was in four cases. In one, the hydrops had completely resolved and the arrhythmia did not recur; in the others there was a recurrence of tachycardia but this was quickly brought under control a second time. Flecainide probably should not be used for atrial flutter because it can increase the ventricular response and therefore increase the heart rate. In the two patients with atrial flutter treated with flecainide, treatment was changed to digoxin after only 2 days in the first patient and in the other patient digoxin had failed to convert or slow the rhythm after 3 weeks with maternal serum concentrations of digoxin at 2 μg/l (patient 1). Some digoxin still present in the fetus may have protected it from adverse effects and potentiated the conversion with flecainide, which occurred within 48 hours.

Thus it is imperative that the type of rhythm disturbance is not treated blindly but is assessed and correctly identified by M mode echocardiography before treatment is started.[12] A further attraction of flecainide is that it can be used for ventricular tachycardias. These are much less common prenatally but do occur,[13] Though in most cases it should be possible to distinguish between atrial and ventricular tachycardias on the M mode echocardiogram, a ventricular tachycardia with retrograde conduction of every beat would be impossible to identify. Other drugs used to treat atrial tachycardias such as digoxin or verapamil are contraindicated for a ventricular tachycardia. Recent reports of sudden deaths in adults treated with flecainide after myocardial infarction are of great concern. We were treating young healthy women but any risk to maternal health must be avoided. The fetus with a tachycardia and severe hydrops is at high risk and therefore potentially dangerous treatment can be considered on its merits but the results of this treatment, which remains experimental at this stage, must be closely evaluated. The evidence from adult studies suggests that poor ventricular function, high drug concentrations, and the presence of cardiac failure are risk factors for the arrhythmogenic effect of flecainide.[14] Our one patient with poor left ventricular function did well and we maintained careful control of drug concentrations. All our fetuses had severe cardiac failure and it is only because they were so compromised that treatment with a high risk drug was considered. Digoxin is the only antiarrhythmic drug with a positive inotropic effect that is safe in the presence of heart failure and this is not adequately or sufficiently quickly transferred by the placenta in most patients. Amiodarone has no negative inotropic effect but it is known to depress thyroid function; this could affect normal development if it occurred prenatally. Studies of an animal model suggested that immature cardiac tissues may be less sensitive to flecainide[15] but this needs to be substantiated in clinical practice.

Initially we attributed the unexplained death in our series to the cordocentesis procedure, but this patient may have died of an arrhythmia induced by flecainide. We performed fetal blood sampling in the past as part of our protocol for the management of hydropic tachycardic fetuses in order to estimate the blood gases, karyotype the fetus, and monitor drug concentrations. We judged that the information gained from this procedure justified the risk (1–2%).[16] The death of patient 5 led us to question this policy and also to re-examine the criteria for the use of flecainide. Our current policy does not include routine fetal blood sampling.

Flecainide proved to be a useful drug in the management of fetal tachycardias. However, its use should be limited to patients with supraventricular tachycardia and those with at least moderate or severe hydrops. Patients must be carefully selected and monitored. In addition, mothers must be fully informed of the risks of treatment. Accurate diagnosis and optimum management depend on treatment by a paediatric cardiologist experienced in the management of arrhythmias and an obstetrician practised in drainage procedures and in obtaining fetal blood samples for blood gas monitoring—for example, where fetal hypoxia is suspected. Use of flecainide is specifically restricted and its role needs to be further assessed in centres where a large database of results can be collected for analysis.

We thank Dr N Rutter for allowing us to include the data from one of his patients in this report.

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CASE REPORTS

Lipomatous hypertrophy of the interatrial septum: an unusual intraoperative finding

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Abstract

Lipomatous hypertrophy of the interatrial septum was an incidental finding in a man of 45 undergoing coronary artery bypass grafting for unstable angina. He was not overweight and did not have any rhythm disturbances. The diagnosis was made on frozen section.

Case report

A 45 year old man presented in August 1989 to the National Cardiac Surgical Unit, Dublin with unstable angina that required emergency grafting.

In August 1988 he had had an inferior myocardial infarction from which he made an uneventful recovery but was left with angina of effort. This remained stable on medical treatment. Two months before operation the angina became unstable and angiography confirmed triple vessel disease. He was a moderately heavy smoker with a family history of ischaemic heart disease: his father died at the age of 51 from a myocardial infarction. Forty eight hours before operation he was admitted to a coronary care unit. He needed intravenous nitrates to control his angina.

He looked fit and was normotensive and in sinus rhythm. There was no evidence of congestive heart failure. He had varicose veins in both legs.

Laboratory investigations were normal except for total proteins (85 g/l (normal range 58–80)); albumin (54 g/l (35–53)); and alanine aminotransferase (45 IU/l (5–35)). The electrocardiogram showed sinus rhythm.

Within hours of his transfer to our unit a coronary artery bypass graft operation was started. Total cardiopulmonary bypass was established through a single aortic cannula and a composite venous cannula after a median sternotomy. Then a lesion of the interatrial septum in front of the right superior pulmonary vein was noticed. At this point bicaval cannulation was carried out and the right atrium was opened to show a firm brownish mass in the interatrial septum.

The mass was regarded as a possible tumour and multiple biopsy specimens were taken for rapid diagnosis from frozen sections to exclude malignancy. Because the appearance of the specimens suggested lipomatous hypertrophy of the interatrial septum we proceeded to do the coronary artery bypass grafting. Before we closed the right atrium we took further biopsy specimens for paraffin sectioning. We used reversed long saphenous vein segments for bypass grafting to the left anterior descending, right coronary, and obtuse marginal arteries.

He came off bypass with no problems other than a transient nodal rhythm which did not affect his haemodynamic state. After operation he remained in sinus rhythm and his remaining hospital stay was uncomplicated.

A paraffin section of the biopsy specimen (figure) showed fragments of normal myocardium infiltrated by mature adipose tissue which surrounded large and small groups of myocytes. The adipose cells were normal and there was no evidence of malignancy. The epicardium contained occasional clusters of lymphocytes. These features are characteristic of lipomatous hypertrophy of the interatrial septum.

Discussion

This is the second case of lipomatous hypertrophy of the interatrial septum detected as an incidental finding at operation. The first was reported by McAllister and Fenoglio in 1978.[1] We believe that this is the first time this tumour-like lesion has been diagnosed by frozen section examination. Accurate histological diagnosis is not difficult if the possibility of lipomatous hypertrophy is borne in mind. Otherwise a low grade liposarcoma is likely to be diagnosed. A firm brown tumour arising in the interatrial septum in a previously fit young man with earlier evidence of arrhythmia certainly did not suggest lipomatous hypertrophy of the interatrial septum. So it was only after it was unequivocally shown that there was no evidence of malignancy in the frozen sections that we continued with bypass grafting.

Lipomatous hypertrophy of the interatrial septum was first reported by Prior in 1964 as an unusual necropsy finding in five patients (mean age 73).[2] Cases have been reported in patients aged 22 to 88 years.[3] In 1971 Hutter and Page reported on the clinicopathological findings in 10 patients and recognised the high incidence of atrial arrhythmias and a deformed P wave on the electrocardiogram (previously described as a "dome and dip" configuration).[4] When we reviewed our patient's past electrocardiograms we found similar P wave characteristics in leads II, III, and aVF in electrocardiograms recorded on

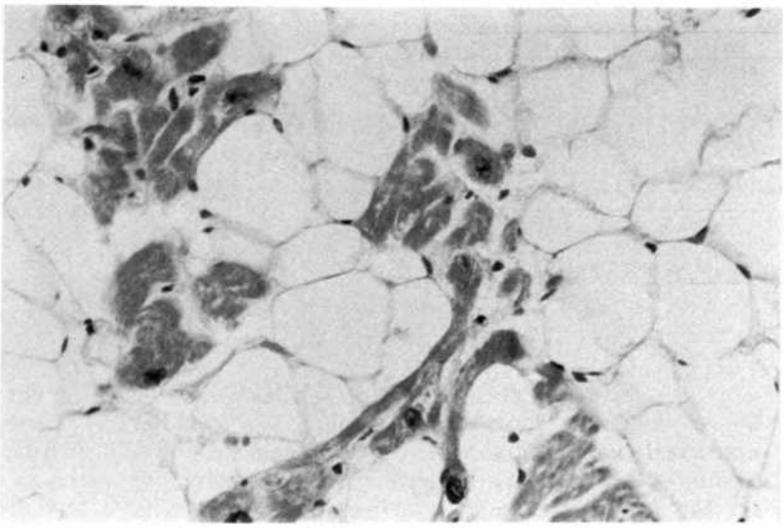

Figure Myocardial fibres surrounded by mature adipose tissue. Haematoxylin and eosin stain; original magnification, × 200.

two occasions before his transfer to us. Such a deformed P wave pattern on an electrocardiogram is often associated non-specifically with atrial enlargement and in our patient because there was no evidence of atrial enlargement it should perhaps have alerted us to the possibility of lipomatous hypertrophy of the interatrial septum.

In 1982 the first report of lipomatous hypertrophy of the interatrial septum in a live patient appeared.[5] This was diagnosed by computed axial tomographic scanning and the pattern of fat deposition was shown. The fat was distributed in a bilobed manner about the fossa ovalis, which itself was spared. The fatty nature of the lesion was apparent from the characteristic Hounsfield number. The cephalad mass of fat was continuous with the subepicardial adipose tissue. Isner *et al* went so far as to suggest that in an obese, elderly patient with supraventricular arrhythmias in whom the cause cannot be identified lipomatous hypertrophy of the interatrial septum should be suspected. Had we suspected lipomatous hypertrophy of the interatrial septum in our patient cross sectional echocardiography would have given us a preoperative diagnosis. Fyke *et al* suggested the following guidelines for making the diagnosis on echocardiography: (*a*) the characteristic bilobed appearance of the atrial septum when the beam is directed through the region of the fossa ovalis; (*b*) a thickness of ⩾15 mm postero-superior or antero-inferior to the valve of the fossa ovalis; (*c*) the absence of any other, more likely explanation for septal thickening.[6] They also add that the presence of P wave abnormalities such as increased voltage and duration or notching supports the diagnosis. Accumulation of septal fat where there is internodal atrial myocardium probably accounts for the reported arrhythmias and P wave configuration.[7,8] Applegate *et al* also reported two patients with lipomatous hypertrophy of the interatrial septum in whom magnetic resonance imaging was done.[9] We know of only one patient in whom lipomatous hypertrophy of the interatrial septum was associated with multiple subcutaneous lipomas.[10] On the other hand, cardiac lipomas, encapsulated masses of mature fat surrounded by myocardium, are known to be associated with berry aneurysms and tuberous sclerosis.

Prior believes that the pathogenesis of lipomatous hypertrophy of the interatrial septum is related to the hypertrophy of normal fatty tissue present in the interatrial septum.[2] McAllister and Fenoglio suggest that it is a hyperplasia of primordial fat.[1] Neither propose a neoplastic process as the essential abnormality.

Our patient will have to be closely followed up because the infiltrative process in lipomatous hypertrophy of the interatrial septum seems to be progressive and symptoms of obstructions may require excision of the lesion.[3]

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Br Heart J 1991;65:51–2

Left anterior fascicular block: an ischaemic response during treadmill testing

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Abstract

A patient in whom exercise induced reversible ischaemic left anterior fascicular block is reported. Glyceryl trinitrate relieved the fascicular block. Coronary angiography showed a 90% obstruction of the left anterior descending artery. The left anterior fascicular block induced by exercise disappeared after a successful coronary angioplasty.

Conduction disturbances during exercise testing are uncommon[1 2] and fascicular blocks are even more rare.[2 3] Four cases of exercise induced, transient, isolated, left posterior fascicular block have been reported,[4] but only two cases of left anterior fascicular block have been described.[3] An association was reported between exercise induced left anterior fascicular block and significant disease of the left anterior descending coronary artery.[3] We report a patient with reversible, isolated left anterior fascicular block caused by ischaemia induced by an exercise test.

Case report

A 47 year old man presented with a history of angina pectoris. No abnormalities were found on physical examination. The resting electrocardiogram and an echocardiographic examination were normal. A graded exercise test was done (CASE II, Marquette, Milwaukee). The patient completed 7·3 minutes of exercise, achieving 8 METS on a Bruce protocol. The test was terminated because of chest pain. Left anterior fascicular block developed at a heart rate of 114 beats/minute, 4 minutes into exercise and reverted soon after exercise stopped. This phenomenon was reproducible on three separate occasions. During the last test, sublingual glyceryl trinitrate was given after the onset of left anterior fascicular block. The block was abolished within a minute while the patient kept exercising and despite a heart rate of 137 beats/minute (fig 1). Hyperventilation increased the heart rate to 120 beats/minute but left anterior fascicular block was not seen. Atropine (2 mg intravenously) also did not cause left anterior fascicular block even though the heart rate rose to 125 beats/minute. Coronary arteriography showed single vessel disease with a 90% stenosis of the luminal diameter of the left anterior descending artery (fig 2). Atrial pacing at rates well above those achieved during exercise did not reproduce the left anterior fascicular block. Percutaneous transluminal coronary angioplasty of the left anterior descending artery was successful (fig 2). A repeat exercise test with the same protocol two weeks later did not induce the left axis deviation despite a peak heart rate of 132 beats/minute. The test was stopped because of fatigue.

Discussion

Bundle branch block during exercise testing is infrequent. Wayne *et al* found exercise induced bundle branch block in 0·39% of stress tests done over a five year period; right bundle branch block was less common than left bundle branch block.[1] Left anterior fascicular block is the least common block induced by exercise: only two cases have been reported.[3] In both cases a severe lesion of the left anterior descending coronary artery was reported. Very similar angiographic findings were seen in our patient. The onset of left anterior fascicular block occurred at low heart rates and the heart rates at the onset and end were similar and reproducible. Atrial pacing

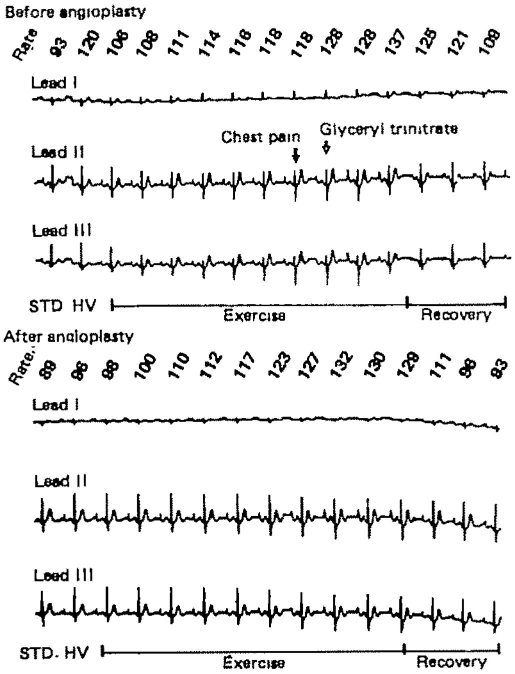

Figure 1 Electrocardiograms from leads I, II, and III during an exercise test before (top) and after (bottom) angioplasty of the left anterior descending artery. Before angioplasty there was left axis deviation. STD, standing; HV, hyperventilation

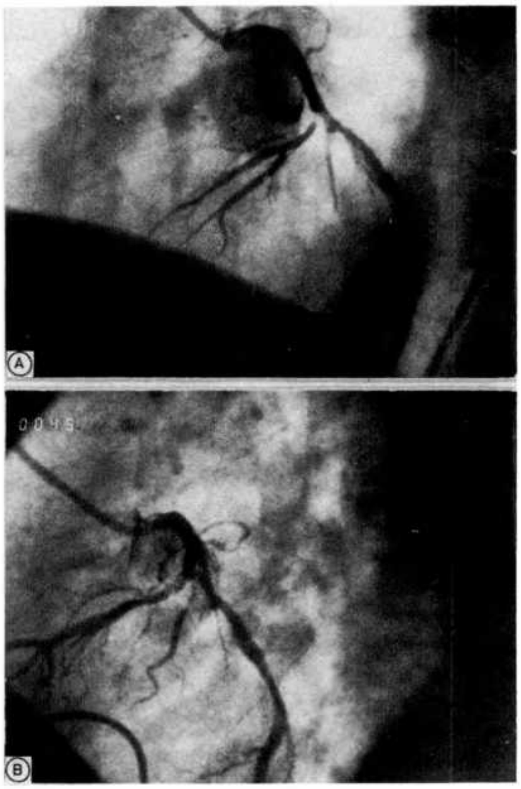

Figure 2 Coronary angiogram of the left coronary artery in the cranial left anterior oblique projection before (A) and after (B) a successful angioplasty.

at rates higher than those achieved at exercise did not induce left anterior fascicular block, which excluded a rate dependent phenomenon.[5] Relief with glyceryl trinitrate and the fact that the block did not recur after angioplasty suggest an ischaemic cause.

The prognosis of isolated left anterior fascicular block at rest is unclear, and that of exercise induced left anterior fascicular block is unknown. Persistent left anterior fascicular block is associated with diffuse His-Purkinjee disease.[6] Experimentally, lesions limited to the left anterior fascicle were insufficient to induce changes in the surface electrocardiogram.[7] Exercise tests are often abnormal in patients with isolated left anterior fascicular block, suggesting that this conduction abnormality might be associated with significant coronary artery disease.[8] It is therefore likely that exercise induced left anterior fascicular block could be an early, reliable marker for diffuse involvement of the conduction system and important coronary artery disease of the left anterior descending coronary artery.

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Prediction of outcome by prenatal Doppler analysis in a patient with aortic stenosis

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Abstract

Stenosis of the aortic valve (pressure drop 50 mm Hg) was diagnosed prenatally by Doppler echocardiography in a 33 week old fetus. Measurement of time-velocity integrals through the tricuspid and mitral valves indicated a significantly higher flow in the right heart. The pressure drop across the aortic valve in the 3 hour old infant was 80 mm Hg. The findings in this patient suggest that the usually accepted theory that prenatally the ventricles function in parallel should take into account the chronology of filling and ejection. In this patient the ability of a ventricle to generate a prenatal transvalvar pressure gradient was evidence that the size, compliance, and contractility of the ventricle were sufficient to maintain good function.

Aortic stenosis is infrequently diagnosed in utero. Most reports are of patients with critical aortic stenosis and poor ventricular dimensions or function or both.[1-3] In such patients it was difficult prenatally to distinguish between aortic stenosis and primary left ventricular myocardial disease or the hypoplastic left heart syndrome and to decide on the best approach to perinatal management.[4]

Methods

Fetal echocardiographic studies were performed with a Hewlett-Packard 77020 ultrasound scanner and a 5 MHz medium focus probe. Doppler ultrasonic intensities were limited to below the 100 mW/cm^2 spatial peak time average. After visualisation of the fetal heart by cross sectional imaging and identification of the best incident angle the continuous wave Doppler probe was used to obtain maximum velocity traces across the aortic valve.

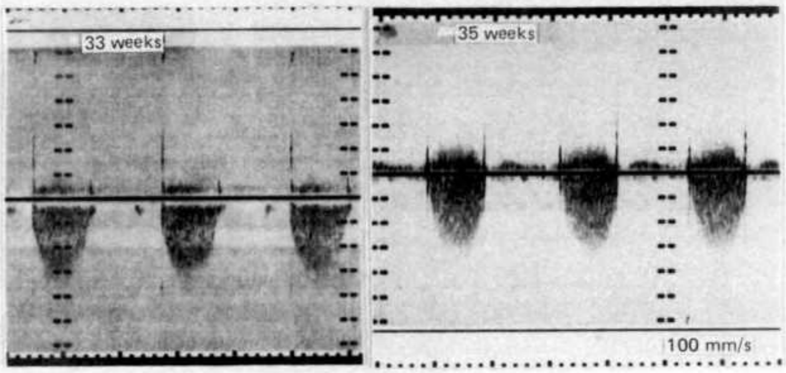

Figure 1 Prenatal diagnosis of aortic valve stenosis in a fetus at 33 and 35 weeks' gestation. Continuous wave Doppler examination shows a peak systolic velocity of 3·5 m/s corresponding to a gradient of 50 mm Hg.

Case report

A woman was referred to our laboratory at 32 weeks' gestation because of a unexplained late fetal death at 36 weeks during a previous pregnancy. The size of the fetus was appropriate for the gestational age and the fetus was in sinus rhythm with a heart rate of 130 beats/minute. There was no evidence of cardiac failure. The ventricular septum was thicker than normal for the gestational age (0·45 cm) (normal range 0·2–0·38[5]). Left ventricular function and dimensions were within the normal ranges. The maximal diameters of the tricuspid and mitral orifices were estimated at 12 mm and 9 mm respectively. Cross sectional echocardiography showed an unusual pulsatile dilatation in the ascending aorta on the anterior wall suggesting a post-stenosis jet lesion. The aortic valve seemed thickened and was dome shaped in systole. Because of the position of the fetus it was impossible to obtain a good Doppler examination of the aortic valve. The mother was therefore re-examined a week later.

At 33 weeks' gestation the fetus was in good position and the maximal transstenotic velocity was 3·5 m/s (fig 1) (corresponding to a mimimum gradient of about 50 mm Hg). No tricuspid or mitral insufficiency was detectable by colour flow Doppler. The fetus was then examined every 2 weeks to monitor progress.

At 35 weeks' gestation the transvalvar gradient was the same. However, time-velocity integrals through the tricuspid and mitral valves were 8·36 cm and 4·92 cm respectively (fig 2). This large difference between the time-velocity integrals when there was only a moderate difference in tricuspid and mitral size indicated a significantly higher flow in the right heart and was predictive of a postnatal increase in gradient. At 38 weeks' gestation and after a normal labour, a male infant (2730 g) with a normal Apgar score was delivered. Examination 3 hours after delivery showed no signs of cardiac failure. A 3/6 ejection systolic murmur was heard; it was maximal at the upper right sternal edge. Doppler echocardiography showed that the min-

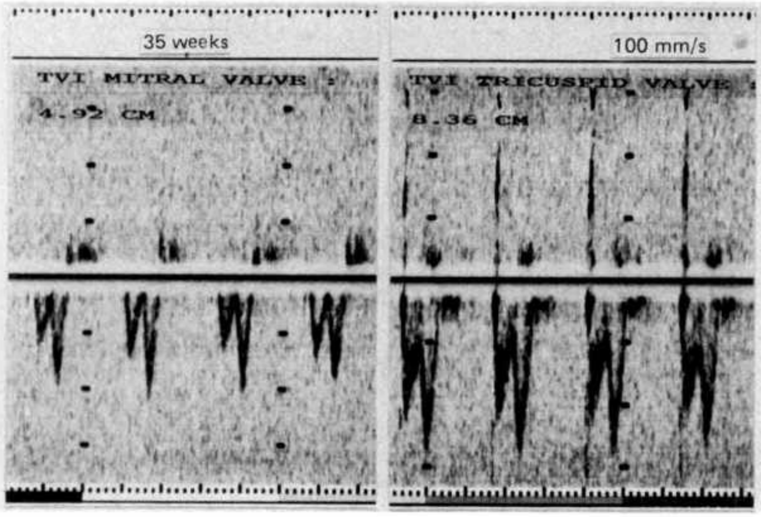

Figure 2 Evaluation of the flow in each ventricle in a 35 week old fetus. The time velocity integral across the mitral valve is 4·92 cm and that across the tricuspid valve is 8·36 cm.

imum gradient across the aortic valve was 80 mm Hg and time-velocity integrals through the tricuspid and mitral valves were 5·73 cm and 7·04 cm respectively. There was a left to right flow through the ductus arteriosus with a maximum velocity of 1·80 m/s. Forty eight hours after birth tachycardia, sweating, and dyspnoea during feeding were noted. A new Doppler evaluation showed the same transstenotic gradient, a small reduction in time-velocity integrals across the tricuspid and mitral valves to 4·49 cm and 6·18 cm respectively, and an increase (to 6 mm) in the thickness of the interventricular septum during diastole. A transventricular valvotomy was performed with a 5 mm Hegar candle. The postoperative gradient was 50 mm Hg without valve insufficiency. At the age of one he was symptom free and growing normally.

Discussion

To our knowledge this is the first reported measurement of a significant transvalvar pressure drop across a stenosed semilunar valve in a fetus. It also shows that such a drop is possible. This suggests that the accepted theory that ventricles function in parallel prenatally may be too simplistic. From this model it follows that when a stenosis is present in one element of the circuit the flow decreases proportionately so that no pressure drop is generated. Because the flow is pulsatile rather than continuous, the systolic and diastolic phases should be considered separately. During the diastolic phase the preload is the same for the right and left ventricles if the flow across the foramen ovale is unrestricted, as is usually the case.[6 7] Differential ventricular diastolic filling mainly depends on the dimensions and compliance of each ventricle. This diastolic filling becomes a major determinant, along with myocardial contractility, of the systolic ejection volume. In the fetus during the systolic phase the afterload is essentially the same for both ventricles. Therefore, the gradient would be determined by the systolic ejection volume and the stenotic surface area.

This model, which takes into account the chronology of filling and ejection, is more realistic and explains the possibility of a considerable transvalvar pressure gradient in a fetus with an intact ventricular septum. In addition, to generate a pressure drop across the semilunar valve the dimensions, compliance, and contractility of the ventricle must be adequate. In our patient the transvalvar pressure gradient of 50 mm Hg was paradoxically a favourable prognostic factor; this accorded with the evidence of good left ventricular function detected during echocardiographic examination of the fetus—that is normal ventricular cavity dimensions and ejection fraction. But measurement of the transvalvar gradient alone is not sufficient to predict the condition in the neonate. This requires evaluation of the flow across the stenotic valve and of the differential flow in each ventricle.

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Br Heart J 1991;**65**:55–6

PRACTICE REVIEWED

Indications for cardiac transplantation

Peter M Schofield

The prognosis of patients with end stage cardiac failure is poor. It can be improved by medical treatment, for example by adding vasodilators[1] or angiotensin converting enzyme inhibitors[2] to diuretic treatment. None the less, the survival rate at 12 months in a group treated with enalapril was only 53%.[2] At Papworth Hospital the cumulative survival rate for patients treated with "triple" immunosuppressive therapy (cyclosporin, azathioprine, and prednisolone) after cardiac transplantation was about 90% at 1 year and 80% at 3 years, which is similar to the experience world wide.[3] Clearly, the quality of life as well as its duration must be considered. This has been shown to be substantially improved by cardiac transplantation, which has a good cost/benefit ratio.[4]

The major causes of mortality in the first year after transplantation are acute graft rejection and uncontrolled infection. After the first year, coronary occlusive disease is the commonest cause of mortality. Advanced occlusive disease, which tends to be diffuse and affects the proximal and distal coronary arteries, may lead to a repeat transplantation being considered.

Cardiac transplantation will continue to be restricted by the limited supply of donor organs.[5] In 1988, around 2500 cardiac transplants were performed in almost 250 international centres; this was only a small proportion of the total population of patients with end stage cardiac failure.

How should we decide which patients should receive the available organs? On the basis of clinical findings and the results of non-invasive and invasive investigations it is usually obvious which patients are severely disabled by left or right ventricular failure or both. The first question is: "is it likely that this patient would return to normal or near-normal activities if their heart was replaced?" Clearly, the procedure is not appropriate if the patient has severe coexisting cerebrovascular disease, peripheral vascular disease, pulmonary disease, or renal disease. In some patients, however, combined organ transplantation may be the preferred option—for example, heart and kidney or heart and liver. Patients accepted for cardiac transplantation should be well motivated and able to cope with immunosuppressive treatment after operation and also the inconvenience of repeated endomyocardial biopsy, particularly in the early postoperative period.

In many transplant centres the upper age limit for the recipient is between 55 years and 60 years. Biological age as well as chronological age should be considered. The age range for recipients of cardiac transplants world wide is 1 day to 78 years and in our unit it is 6 to 63 years.[3] At Papworth Hospital the age limit is around 55 years for the patients with coronary artery disease and around 60 years for those with dilated cardiomyopathy. This is because in the early postoperative period vascular complications, particularly cerebrovascular events and gastrointestinal ischaemia, are more common in the more elderly patients with coronary artery disease.

Most of our patients undergoing cardiac transplantation had heart failure refractory to medical treatment associated with either coronary artery disease (53%) or dilated cardiomyopathy (44%). This resembles experience world wide—43% and 49% respectively.[3] The timing of cardiac transplantation may be difficult in some patients. The symptoms of cardiac decompensation in patients with coronary artery disease usually remain stable, unless there is an event causing further myocardial damage, and sudden death is a continuing risk. In contrast, the condition of those with dilated cardiomyopathy can deteriorate quite rapidly, or in some cases improve, making their assessment for cardiac transplantation and the timing of surgery even more difficult. Therefore, careful and frequent follow up is required for each patient. The remaining group of patients undergoing transplantation—in our series, 3% of the total population—includes those with other types of cardiomyopathy (for example, hypertrophic or restrictive), end stage valve disease, severe angina caused by coronary artery disease that is not amenable to revascularisation, and patients with ventricular tachycardia that is refractory to other forms of treatment. Occasionally, therefore, it may be appropriate to give a cardiac transplant to a patient who is severely limited by angina rather than by the symptoms of cardiac failure—if they are unsuitable for coronary angioplasty or bypass surgery. Patients with ventricular tachycardia that is refractory to drug treatment, many of whom have considerable left ventricular dysfunction, are an interesting group. Transplantation should be considered in those who are severely restricted by symptoms of cardiac failure. For those with life threatening tachycardia but no cardiac failure the relative cost/benefit of implantable cardioverter-defibrillators and

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cardiac transplantation could be established in a randomised, controlled trial.

In our experience about 6% of patients referred with a view to cardiac transplantation are suitable for "conventional" cardiac surgery. This is usually either left ventricular aneurysmectomy or mitral valve surgery, with or without myocardial revascularisation. Clearly, cardiac catheterisation will establish the cause of heart failure and will determine whether any conventional treatment would be of benefit. A fixed, raised pulmonary vascular resistance in excess of 5–6 Wood units that does not fall when the oxygen saturation is increased is an absolute contraindication to orthotopic cardiac transplantation. The pressure drop across the pulmonary vascular bed (mean pulmonary artery pressure minus mean left atrial pressure) is a useful measurement, particularly if the data on cardiac output are unreliable; and at Papworth Hospital we believe that a value of more than 15 mm Hg should preclude orthotopic transplantation. In patients with raised pulmonary vascular resistance who undergo transplantation, acute right ventricular failure commonly occurs in the early postoperative period.[6 7] Clearly, pulmonary vascular resistance can change so every 4–6 months we reassess patients awaiting assessment for transplantation or awaiting surgery, particularly those in whom resistance is at the upper end of the accepted range.

Heart-lung transplantation may have to be considered in patients who have a fixed, raised pulmonary vascular resistance. An alternative is the "domino" procedure in which the heart from a heart-lung recipient (for example who has primary pulmonary hypertension or cystic fibrosis), which has a pre-stressed right ventricle, is used. In theory, such hearts may be suitable donor organs for the group of patients with a raised pulmonary vascular resistance, though experience is too limited to make definitive conclusions.

Most recipients and donors of cardiac transplants are male. In our unit 89% of recipients and 74% of donors are male (83% and 70% world wide respectively).[3] The donor and recipient are matched for blood group and size. The risk of postoperative complications is higher in grafts from female donors.[8] This is partly because female recipients, a high proportion of whom receive grafts from female donors, are more likely to suffer fatal rejection. In addition, the risk of graft loss from coronary occlusive disease is higher in female donor grafts in male recipients.

The use of mechanical circulatory support devices as a "bridge" to cardiac transplantation has increased.[6] While the results of surgery in this group continue to improve, they generally have not been as good as in patients who do not require mechanical support preoperatively; so this is probably not the best use of available donor organs. Similarly, the results of repeat cardiac transplantation are not as good as those for the first operation. We often face a conflict between the needs of an individual patient and the overall best use of available organs.

There is no doubt that cardiac transplantation is a highly effective treatment for many patients with end-stage cardiac failure. The gap between the demand for transplantation and the supply of organ donors is likely to increase. We must make the best use of the organs available and aim to have as many donor organs as possible functioning 5 or 10 years after transplantation. We must work towards preventing the occurrence of advanced coronary occlusive disease several years after cardiac transplantation because this too will increase the demand for donor organs.

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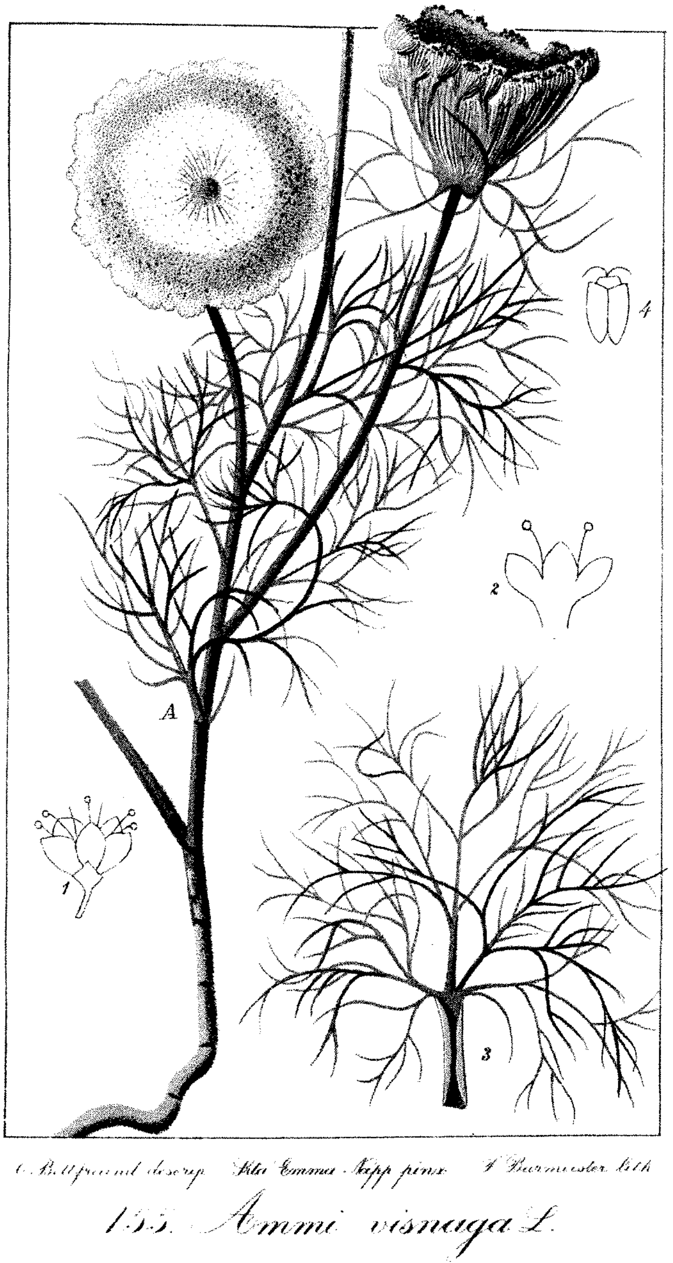
PLANTS IN CARDIOLOGY



Ammi visnaga (L.) Lam. Bettfreund C. *Flora Argentina*. 1901: plate 155.

Royal Botanic Gardens Kew.

Amiodarone, nifedipine, sodium cromoglycate

Ammi visnaga is a herbaceous Mediterranean plant belonging to the family Umbelliferae, named after *umbra* a shadow or shade. The binomial name is from antiquity and has no special meaning while in Egypt the plant is called khella. When dried the stout flower stalks were used as toothpicks hence the early French name, "herbe aux curedents".

People living on the Nile delta often had renal stones because urinary schistosomiasis was common. For many centuries khella, which is common in the delta, was known to relieve renal colic. The seeds (fruits) contain the active principle khellin—first extracted in 1879 and identified at Cairo University in 1932 as a chromone. Khellin works by relaxing the smooth muscle of the ureter.

It was, however, a chance observation in 1945 by G V Anrep, a pupil of both Pavlov and Starling, that led to the development from khellin of modern drugs for asthma and heart disease. Anrep was Professor of Pharmacology in Cairo and his technician who had severe angina got renal colic and treated himself with khella. When the man returned to work Anrep perceptively noticed that he no longer had angina and this stimulated him to investigate the effect of khellin on the heart. Using the heart-lung preparation Anrep measured the coronary blood flow in dogs and showed that khellin was an effective and selective coronary vasodilator. Then he did a clinical trial in patients with angina which gave favourable results. His seminal paper reporting these findings was published in the *British Heart Journal* (1946;**8**:171–7.)

This stimulated research elsewhere; and in Belgium the work of R Charlier and J Broekhuysen, who prepared hundreds of compounds with emphasis on the benzofurane portion of khellin, led in 1961 to the synthesis of amiodarone. The name is derived from *am*, to indicate the presence of an amine function; *iod*, for the iodine moiety; and *arone* from benziodarone, an earlier drug in the ketonic benzofurane group.

F Bossert, working for the Bayer company, decided to use khellin as the starting point for his endeavour to find a coronary vasodilator that worked intravenously as well as orally. After 16 years' work he found a promising dihydropyridine compound and two years and 2000 derivatives later he and Vater produced nifedipine. In Britain Anrep's work catalysed research for a new bronchodilator and sodium cromoglycate, Intal, resulted from the work of an asthmatic doctor, Roger Altounyan, who did all the experiments on himself. Paradoxically its unique mode of action is to prevent the release of mediators of bronchoconstriction and not by bronchodilatation.

Several species of Umbelliferae contain fumocoumarins that are photosensitisers and greatly enhance the action on the skin of ultraviolet radiation. An important one is present in *Ammi majus* L. called ami by Galen and known in Egypt as regl el ghorab. It is a psoralen called methoxsalen and when given orally with long wavelength (ultraviolet A) radiation it constitutes PUVA therapy. This has achieved considerable success in treating psoriasis (long known to improve with sunlight) and also vitiligo, and is useful in mycosis fungoides. Some umbellifers such as *Pastinaca sativa* (wild parsnip) are notorious for producing severe contact dermatitis in sunlight, which reminds one of the photosensitivity of amiodarone. As a genus *Ammi* must be unsurpassed as a source of important medicines.

A HOLLMAN

BRITISH CARDIAC SOCIETY NEWSLETTER

The British Cardiac Society is moving, but not far. Number 7 St Andrew's Place has been our home for five years. It is convenient for the college, and the proximity has become increasingly appreciated as we have made joint cause to resist inappropriate changes in numbers and programmes for our trainees. But the premises became too small, a problem that has been exacerbated by the increasing activities of the society. We have been offered and accepted space that is contiguous at the top of numbers 1 and 2 in the same attractive regency terrace. This change will give us about twice as much room. Health conscious cardiologists will be spared the corrupting temptation of a lift and can continue to combine business with the pleasure of exercise as they visit the new offices. We will be able to hold council and other important meetings on our own premises instead of accepting the kind hospitality of the college whenever we have gatherings of more than five or six people. We will change our address sometime in January. Our telephone and fax numbers remain the same.

Members of the society understand that we must become more active if we are to play an appropriate role in these times of change and challenge. Most of the new work can best be undertaken by committees. Already four have been set up (data management, training and manpower, publications and journals, and audit) and a fifth is being created (technicians). We will meet the immediate objectives for our reorganisation with the addition of two more that have now been approved by council. A medical practice committee will be concerned primarily with guiding members on matters of good medical practice. We have already been asked by members to provide advice on whether certain management policies that have aroused some controversy could be supported if they were to be challenged in this litigious age. We should be able to provide a consensus view that will carry weight, and thereby a measure of protection. Sometimes the committee could take the initiative and offer advice if difficulties can be foreseen. We also envisage the possibility that the committee could coordinate clinical research under the aegis of the society, particularly of a nature that may not bring support from grant giving bodies or the pharmaceutical industry. Kim Fox will be chairman, and he will be supported by Julian, Hubner, Cobbe, Camm, and the President.

The second new committee will operate in a more sensitive area. We hope that members will appreciate the need for an Ethical and Legal Committee, and will support its aims. We believe on the one hand that the profession has an obligation to help patients obtain a fair outcome in any claims relating to treatment, and on the other that colleagues should be protected against mischievous claims supported by spurious or ill advised medical evidence. Lawyers often find difficulty in obtaining objective help from experienced and respected members of our specialty. As a result they sometimes turn to those whose knowledge may not be relevant to the matter in question, and rarely may even be driven to seeking help from the tiny minority whose motives may not be based purely on justice. The committee will encourage members of the society to allow their names to be sent to the Law Society as a panel that would be available to give advice on matters within their areas of competence. The scheme has not been finalised and more discussions and more advice are needed before we have firm proposals. Members of the panel could avoid the inappropriate fear of opprobrium from their colleagues because all will be aware of the society's endorsement of their tasks. None of us feels comfortable in this role, and no doubt service on the panel would be for a limited period only. This proposition has been discussed previously, but was shelved on the advice of the General Medical Council which sought clarification on some matters of detail. We now have approval from the council subject only to caveats that we would in any case wish to follow. The Chairman of the Council's Standards Committee "... is of the opinion that no exception could be taken on ethical ground to the sending of a list of senior cardiologists, prepared to undertake medico-legal work, to the Law Society, or indeed to the Bar Council or to individual barristers or firms of solicitors ... your society will take steps to ensure that the list contained only the names of doctors who were fully qualified to undertake this kind of work, and ... that no list should be presented in such a way as to imply exclusivity ...". The full text of the letter can be obtained from the society's office. Initially the committee will comprise Keith Fox (chairman), Kim Fox, Michael Petch, Raphael Balcon, Stewart Hunter, and Roger Hall together with the President. This group will prepare detailed proposals for endorsement by the society. The Royal College of Obstetricians and Gynaecologists announced a similar scheme a few months ago. Though the Cardiac Society may have been the first to discuss this development we will not now be the first to implement it.

This is not quite all. Cardiologists in Britain have tended not to espouse the cause of so-called prevention. We cannot then complain if the arena is left to those in other disciplines who may seem less critical of strategies than we would wish to be. Perhaps the name itself has been a disincentive because it suggests an aim that seems to us unrealistic. We will take a more active interest. The council have approved the creation of an epidemiology and risk reduction advisory group to be chaired by David Wood, joined by Hugh Tunstall-Pedoe, Michael Scott, and the President. More names may be added later. Finally, council warmly endorsed a request from the new British Paediatric Cardiac Group to be affiliated to the British Cardiac Society. This is the fifth affiliated group and it joins those for pacing and electrophysiology, interventionalist cardiology, nuclear cardiology, and echocardiography. The officers are Hunter (president), Tynan (vice president), Qureshi (secretary), and Anderson (treasurer), with Deanfield, Sethia, Keeton, and Duff as committee members.

We have much more to write but we have used our allotted space. No doubt you will await eagerly the February newsletter which will contain more news and views that you will not want to miss.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society,
7 St Andrew's Place,
London NW1 4LB

NOTICES

British Cardiac Society
The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow, on 30 April to 3 May 1991. The closing date for receipt of abstracts was 10 December 1990.

Training of paramedic ambulance staff
A one day Seminar for Trainers and Potential Trainers of Paramedic Ambulance staff will be held by the College of Anaesthetists in the Royal College of Surgeons on 7 February 1991. The subjects to be covered are multidisciplinary and include the present situation, candidate selection, the syllabus, problems and logistics, medico-legal aspects, audit, and relationships with general and hospital practitioners. Registration fee to include coffee, lunch, and tea—£20. Applications to Mr Stanley Alan, College of Anaesthetists at the Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Arrhythmias and valvular heart diseases
A meeting of the European Society of Cardiology Working Group on Valvular Heart Diseases entitled "Arrhythmias and Valvular Heart Diseases" will be held in Namur on 24 and 25 May 1991. For information write to Professor R Krémer, Meeting ESC, Arrhythmias and Valvular Diseases, University Hospital de Mont-Godinne, B-5530 Yvoir, Belgium.

Echocardiography and Doppler in cardiac surgery
The Fourth International Symposium on Echocardiography and Doppler in Cardiac Surgery will take place in Innsbruck on 27 to 29 May 1991. Further information from Dr G Maurer or Dr W Mohl, c/o Interconvention, A-1450 Vienna, Austria.

Br Heart J 1991;65:59–60

CHECKLIST

Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.

General

Three complete sets of the manuscript (with 3 sets of figures) are submitted (this also applies to amended versions). ☐

The manuscript is typed double spaced throughout on one side only on A4 opaque white bond paper with wide margins all around. ☐

The manuscript is arranged as follows: (1) title page, (2) abstract, (3) text, (4) references, (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1. ☐

The last name of the first author is typed at the top right corner of each page. ☐

A covering letter is signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. ☐

Title page

The title and authors' names are typed on the title page. ☐

Case reports have only three authors. ☐

The address(es) of the institutions from which the work originated with the authors' names are listed underneath. (If there is more than one address several authors' names can be grouped under each appropriate address; strict order of authors' names is not necessary here.) ☐

The full name, exact *postal* address with postal code, and telephone number of the author to whom communications and proofs should be sent are typed at the bottom, and the editorial office must be told of any subsequent changes of address. ☐

Abstract

An abstract is typed double spaced on a separate page. ☐

The abstract is organised according to the framework described on page 1 of the January 1991 issue. In exceptional cases this may not be necessary—for example, case reports. ☐

Abbreviations other than standard SI units of measurement are not used. ☐

Text

Appropriate headings and subheadings are provided. ☐

Every reference, figure, and table is cited in the text in numerical order. (Order of mention in text determines the number given to each.) ☐

Acknowledgments and details of support in the form of grants, equipment, or drugs are typed at the end of the text, before references. ☐

References

References are identified in the text by arabic numerals; no more than three references are cited for any one statement. ☐

References are typed double spaced on sheets separate from the text (*numbered consecutively in the order in which they are mentioned in the text*) in the Vancouver style. ☐

Journal references contain *inclusive* page numbers; book references contain *specific* page numbers. ☐

Citations of abstracts and letters should be indicated in parentheses. ☐

Personal communications, manuscripts in preparation, and other unpublished data are not cited in the reference list but are mentioned in the text in parentheses. ☐

Abbreviations of journals conform to those used in *Index Medicus,* US National Library of Medicine. The style and punctuation of the references follow the format illustrated in the following examples: ☐

Journal: (list *all* authors if six or less; otherwise list first three and add *et al*; do not use full stops after authors' initials)

31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angiographic findings. *Br Heart J* 1984;52:304–8.

Chapter in book:

28 Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. *Heart disease in infants, children and adolescents.* Baltimore: Williams and Wilkins, 1968:134–9.

Book (personal author or authors): (all book references should have specific page numbers)

36 Feigenbaum H. *Echocardiography.* 3rd ed. Philadelphia: Lea and Febiger, 1981:549–63.

Figure legends

Figure legends are typed double spaced on sheets separate from the text, and figure numbers correspond with the order in which figures are presented in the text. ☐

All abbreviations appearing on the figures are identified at the end of each legend. ☐

Written permission from the publisher and author to reproduce any previously published figures is included. ☐

Figures

Three sets of unmounted glossy prints (not originals) of each photograph and drawing are submitted in three separate envelopes. ☐

Figures, particularly half tones and electrocardiographic tracings, have been submitted with the following guidelines in mind: the detail on the figure is sufficiently clear to withstand reduction and special features are designated by arrows. ☐

Black ink is used for all line drawings. Decimals, lines, etc *must* be strong enough for reproduction. ☐

The first author's last name, figure number, and "top" are indicated on the back of each illustration in light black pencil, preferably on a gummed label. ☐

Figure title and caption material appear in the legend not on the figure. ☐

Figures are limited to the number necessary for clarity and do not duplicate data given in the tables or text. (Estimates for colour work will be provided on acceptance of the manuscript for publication. Some of the cost of colour printing will be charged to the author(s).) ☐

Tables

Tables are typed double spaced on separate sheets with the table number and title above the table and explanatory notes below. The table numbers are arabic and correspond with the order in which the tables are presented in the text. ☐

A footnote to each table identifying all abbreviations used is given in alphabetical order. ☐

Tables are self-explanatory, and the data are not duplicated in the text or figures. ☐

Written permission from the publisher and author to reproduce any previously published tables is included. ☐

Ethical standards

The study complies with the Declaration of Helsinki. ☐

The research protocol has been approved by the locally appointed ethics committee and the informed consent of the subjects (or their parents) has been obtained. ☐

Measurements and abbreviations

Measurements are given in SI units. ☐

Abbreviations or acronyms are always written out in full (for example, ECG, electrocardiogram; LVH, left ventricular hypertrophy; CAD, coronary artery disease, MI, myocardial infarction). ☐

Only units of measurement and mathematical formulas and calculations are abbreviated and they follow the form recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Br Heart J* 1984;**51**:1–6). ☐

Statistics

If the same variable is measured by two different methods the agreement between the methods has been assessed according to the guidelines published in the *British Heart Journal* (1988;**60**:177–80). ☐

Statistical measures of variation, such as SD or SEM, are specified and given in parentheses. ☐

Papers that do not adhere to these instructions will be returned for revision before assessment.

Br Heart J 1991;65:63-7

ORIGINAL ARTICLES

Mechanism of shock associated with right ventricular infarction

J E Creamer, J D Edwards, P Nightingale

Abstract

Various mechanisms have been proposed to explain the shock sometimes associated with right ventricular infarction, but only small numbers of patients with clinical shock have been studied. The haemodynamic profiles of seven patients with clinical cardiogenic shock after right ventricular myocardial infarction were studied prospectively. They were selected because all had a stable cardiac rhythm and none had absolute hypovolaemia during the study period. In all of them the mean right atrial pressure exceeded the pulmonary artery occlusion pressure. After treatment with varying combinations of dopamine, dobutamine, and glyceryl trinitrate (titrated to achieve the optimum haemodynamic response) the mean systemic arterial pressure increased, as did the cardiac index. There was an associated increase in the left ventricular stroke work index but the right ventricular stroke work index was unchanged. There was no significant change in heart rate, mean right atrial pressure, or pulmonary artery occlusion pressure. This suggests that the probable mechanism of the shock associated with right ventricular infarction is concomitant severe left ventricular dysfunction.

Necropsy studies reported in 1948 showed that the right ventricle was often affected in patients with myocardial infarction,[1 2] but the clinical syndrome of right ventricular dysfunction associated with inferior myocardial infarction was not fully described until 1974.[3] It correlated with extensive involvement of the right ventricle. Subsequently it became apparent that right ventricular infarction may be associated with a range of haemodynamic states.[4 5]

The frequency of shock associated with right ventricular infarction may be underestimated[6] but this subgroup of patients with cardiogenic shock has been shown to have a better prognosis and has therefore attracted specific attention.[7 8]

Several mechanisms of shock in right ventricular infarction have been proposed but their importance has been difficult to assess because this is an unstable condition that requires urgent treatment and does not always allow the rigid application of investigative protocols. Arrhythmias are common in right ventricular infarction and, when present, make an obvious contribution to the development of shock.[9] Inappropriate administration of diuretic or vasodilator drugs can also precipitate shock.[10 11] Mechanical complications such as rupture of the ventricular septum or free wall and acute mitral regurgitation can produce shock whereas the contributions of tricuspid regurgitation and septal dysfunction are unclear. Hypoxia, by inducing pulmonary hypertension, is probably a significant factor in most patients.[8] In other patients, though right ventricular dysfunction is regarded as a major cause, particularly in the context of left ventricular filling,[11] the main debate has been over the contributions of hypovolaemia and concomitant left ventricular dysfunction.[12]

There have been many studies of right ventricular infarction but there are few systematic studies of right ventricular infarction with shock. To define the mechanism of shock associated with right ventricular infarction we examined the haemodynamic profiles of a specific subgroup of patients both before and after successful resuscitation.

Patients and methods

We prospectively studied seven patients (four men; mean age 62, range 46 to 74 years) (table) who fulfilled the clinical criteria for cardiogenic shock after transmural inferior myocardial infarction that persisted despite controlled volume replacement where appropriate.

Shock was defined as hypotension (cuff systolic blood pressure < 80 mm Hg) with signs of hypoperfusion (disturbance of conscious level and oliguria with < 20 ml urine per hour), and a cardiac index of < 1 8 l/min/m^2.[13] Right ventricular infarction was diagnosed on the basis of electrocardiographic features of acute inferior transmural infarction and associated increases in serum concentrations of creatine kinase and aspartate transaminase, raised jugular venous pressure with paradox, and the absence of clinical and radiological evidence of pulmonary oedema. In all cases invasive monitoring showed raised right atrial pressure that exceeded the pulmonary artery occlusion pressure; there was a steep 'y' descent in the right atrial pressure waveform and an early diastolic "dip" in the right ventricular pressure trace.[13-15] During the study period 15 patients with shock and right ventricular infarction, as orginally described, were managed on this unit. The patients reported here were chosen because they had no change in cardiac rhythm between measurements; none had any

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2 October 1990

Clinical data on patients

Case	Sex	Age	Previous infarct	Other diseases	Drugs	Maximum concentration (U/l) CK	AST	IPPV	Arrhythmia	Inotrope (μg/kg/min)	Outcome
1	M	71	—	—	—	3257	358	–	CHB	DA 12 5	S
2	M	48	—	—	—	4962	500	+	—	DB 42·7	S
3	M	46	Anterior	CABG	GTN	3144	295	+	—	DB 13 5	S
4	F	74	—	Previous AF	—	2885	319	+	AF, VT CHB	DA 4 0	S
5	F	72	—	Hypertension, angina	meDOPA, nifedipine	476	221	+	CHB, AF	DA 6 0	Died
6	M	59	—	Intermittent claudication	—	1697	264	+	VF	DA 8 0	S
7	F	62	Anteroseptal	—	—	5280	850	+	AF, CHB VF	DA 20 2	S

AF, atrial fibrillation, AST, aspartate aminotransferase, CABG, coronary artery bypass grafting, CHB, 3rd degree atrioventricular block; CK, creatine kinase; DA, dopamine, DB, dobutamine, GTN, glyceryl trinitrate, IPPV, intermittent positive pressure ventilation, Max, maximum, meDOPA, methyldopa, Min, minimum, S, survivor, VF, ventricular fibrillation, VT, ventricular tachycardia

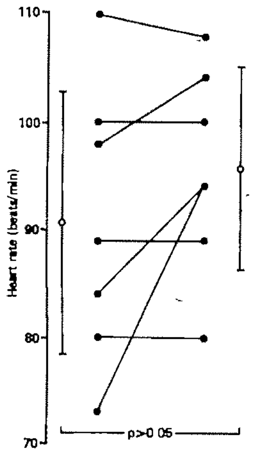

Figure 1 Heart rate (mean (1 SD)) before and after reversal of shock.

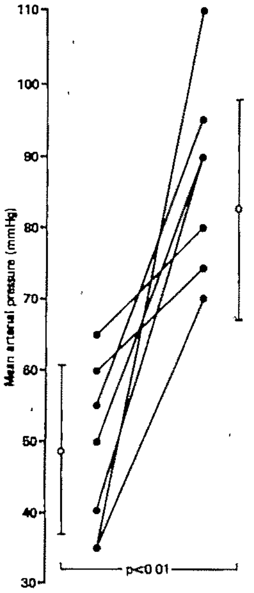

Figure 2 Mean arterial blood pressure (mean (1 SD) before and after reversal of shock.

evidence of mechanical complications from their infarction or pre-existing respiratory disease. No patient had been treated with diuretics, vasodilators, thrombolytic drugs, β adrenergic blocking agents, or other negatively inotropic agents immediately before the onset of shock. There was no change in mode of ventilation during the study.

The time from onset of myocardial infarction to the onset of shock ranged from four to 104 (mean 41) hours.

HAEMODYNAMIC MEASUREMENTS

All patients had pulmonary artery balloon flotation catheters and femoral arterial catheters inserted by one of us to monitor treatment and to measure intravascular pressures (7000 series bedside monitors, Marquette Electronics, Milwaukee, Wisconsin). We measured right atrial pressure, pulmonary artery occlusion pressure, and mean arterial pressure. Cardiac output was measured by a standard thermodilution method with a cooled injectate (< 10°C). Stroke volume index, systemic vascular resistance, left ventricular stroke work index, and right ventricular stroke work index were calculated from standard formulas.

MANAGEMENT PROTOCOL

The patients were managed according to a protocol that was agreed before the study. Priority was given to the correction of hypoxia (for which six patients needed mechanical ventilation), pacing for complete heart block (four patients), and DC countershock (two patients with ventricular fibrillation and one with ventricular tachycardia) Pulmonary and femoral arterial catheters were inserted as soon as possible and modified fluid gelatin or glyceryl trinitrate was infused, where necessary, to produce an optimum pulmonary artery occlusion pressure of 16 to 18 mm Hg.[16 17] For the purpose of this study a full set of haemodynamic measurements was made at this stage and no further fluid load was given. At this point all patients had persistent clinical and haemodynamic features of shock, as defined above, and required additional inotropic support. They were treated with intravenous infusions of either dopamine or dobutamine. Initial doses of dopamine were 2 5 μg/kg/min, and dobutamine 5 μg/kg/min; these were adjusted according to frequent measurements of cardiac output to give a cardiac index approaching 2·2 l/min/m^2,[13] mixed venous oxygen saturation of ≥60%, and reversal of the clinical features of shock as previously described.[18] When these goals had been achieved the haemodynamic measurements were repeated.

Haemodynamic variables before and after treatment were compared by Student's t test for paired samples, supplemented by the Wilcoxon signed rank test where the distributions were in doubt (left ventricular stroke work index, systemic vascular resistance).

Results

Figures 1–4 show the initial haemodynamic measurements and those after reversal of shock. There was no significant change in heart rate when shock was reversed but there were significant increases in mean arterial pressure, stroke volume index, and cardiac index.

There was no significant change in mean systemic vascular resistance, which was 897 (340) dyn.s.cm^{-5} before treatment and 1052 (186) dyn.s.cm^{-5} after treatment. Figure 5 shows the change in left and right ventricular stroke work index associated with reversal of shock and its relation to the preload of the respective ventricle. There was no significant change in right atrial pressure (21 (3) mm Hg before and 23 (3) mm Hg after treatment) or pulmonary artery occlusion pressure (17 (4) mm Hg before and 19 (3) mm Hg after treatment). Left ventricular stroke work index increased significantly on reversal of shock whereas right ventricular stroke work index was unchanged.

Discussion

Studies of right ventricular infarction are common whereas those of shock are scarce.[19 20] All the patients we studied had shock after right ventricular infarction, which was diagnosed on the basis of the electrocardiographic changes of inferior infarction and the clinical and haemodynamic signs of right ventricular dysfunction in addition to those of shock. The use of radionuclide or contrast angiographic studies to confirm the diagnosis was not feasible or appropriate in the initial unstable phase of shock during which the studies were performed, but echocardiography was used to ex-

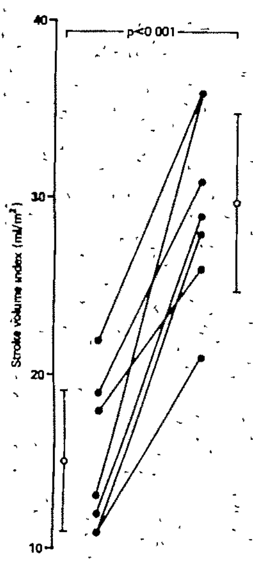

Figure 3 Stroke volume index (mean (1 SD)) before and after reversal of shock.

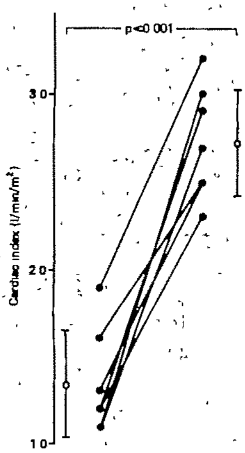

Figure 4 Cardiac index (mean (1 SD)) before and after reversal of shock.

clude mechanical complications of infarction. Previous reports using such methods for the diagnosis of right ventricular infarction concentrated on less ill patients, though occasional patients with shock were included.[21] The small number of patients in the present study was unavoidable because of the entry criteria and the difficulty in controlling a study protocol in unstable and critically ill patients. The study was performed before the introduction of routine thrombolytic treatment.

Because all the patients had a stable cardiac rhythm during the study period, the contribution of arrhythmia to the shock state was minimised. Similarly, the potential vasoconstrictive effects of hypoxaemia on the pulmonary vascular bed were minimised by prompt correction of hypoxia, by mechanical ventilation, where necessary, before any other treatment. At the time of the study it was not possible to assess specifically the potential influence of acute secondary tricuspid regurgitation or of paradoxical septal motion or right ventricular dilatation in producing shock; but the lack of improvement in right ventricular function when shock was reversed suggests that these factors are unlikely to have contributed significantly.

Hypovolaemia in acute right ventricular infarction can be absolute if there have been excessive fluid losses because of sweating, vomiting, or the inappropriate use of diuretics.[8 10] It may also be relative because the optimal left ventricular filling pressure is higher than normal during acute infarction. Allen *et al*, relying on central venous pressure monitoring, found relative hypovolaemia in 20% of patients with cardiogenic shock after myocardial infarction and improved their clinical state by the infusion of up to 300 ml of crystalloid hourly.[11] Others have sought to improve cardiac performance in acute myocardial infarction by fluid volume expansion controlled by measurement of the left ventricular filling pressure. Russell *et al* suggested that the optimum left ventricular end diastolic or pulmonary artery disastolic pressure was 20–24 mm Hg.[22] Of the 19 patients studied, however, only three were hypotensive. Five patients had no improvement in stroke index with increasing filling pressure, four of these had overt heart failure, and four of this group died. The "optimum" filling pressure was therefore defined for the patients with less severe left ventricular dysfunction but was not clear for this latter group and therefore its application to patients with shock could be considered inappropriate.

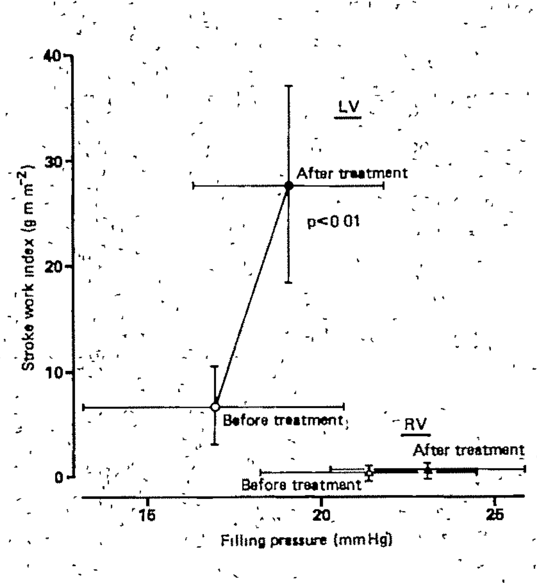

Figure 5 Relation of stroke work index to filling pressure (mean (1 SD)).

Crexells *et al* measured pulmonary artery occlusion pressure in 23 patients with myocardial infarction (12 with pulmonary congestion and five with cardiogenic shock) and found the optimum to be 14–18 mm Hg.[17] The cardiac index and stroke work index could be improved by fluid volume expansion only when the initial pressure was <14 mm Hg. They also found that right ventricular function was improved by increased right atrial pressure but only for increases of up to 6–8 mm Hg. The anatomical site of infarction was not specified in this study. A recent study of volume loading and glyceryl trinitrate administration in right ventricular infarction suggested that the optimal filling pressure of the right ventricle was 10 to 14 mm Hg.[23] Above this value right ventricular stroke work index declined. In patients with shock after right ventricular infarction the right ventricular filling pressure is almost invariably higher than this.

In occasional patients with right ventricular infarction and shock, fluid volume expansion alone restored normal systemic perfusion. This is a rare effect in patients who have not previously received diuretics.[8] Because of the design of the present study achieving an optimum left ventricular filling pressure alone was insufficient to reverse the haemodynamic and clinical features of shock, and in all cases additional inotropic support was required.

The role of right ventricular dysfunction in the production of shock was suggested in early reports of right ventricular infarction. This was based on the assumption that any associated left ventricular dysfunction was modest because pulmonary artery occlusion pressures were low and the condition apparently responded well to administration of fluid. It has been suggested that the reduced pump function of the right ventricle may impair left ventricular filling.[24 25] A study of prognosis of postinfarction ventricular septal rupture found a higher mortality in patients with inferior infarctions.[26] Shock was more common in patients with inferior infarctions and it correlated with mortality; from this it was suggested that right ventricular dysfunction was responsible. Indirect methods were used to assess the function of each ventricle, however, and the role of right ventricular dysfunction in the production of shock was not established.

In right ventricular infarction, if pulmonary arterial hypertension is not present because of hypoxia, there is a progressive pressure gradient from right atrium through right ventricle and pulmonary arteries to pulmonary veins and left atrium that allows passive blood flow.[12 27] Furthermore, the pressure waveforms in right atrium, ventricle, and pulmonary artery are often indistinguishable in acute right ventricular infarction (which may require fluoroscopy to position the pulmonary arterial catheter) suggesting that passive flow may indeed occur. In the present study the reversal of clinical shock with improvement in cardiac output and with increases in left ventricular stroke work index strongly suggest that reversal of shock was brought about by improvement in left ventricular function and that the shock was primarily related to this dysfunction.

In this clinical study of patients in cardiogenic shock we were unable to study the causes of this left ventricular dysfunction but we can postulate possible mechanisms. Firstly, as originally shown in necropsy studies, isolated right ventricular infarction occurs in only 2–4% of cases.[1 2] There is almost always concomitant disease of the left coronary artery with varying degrees of left ventricular infarction. This leads to loss of contracting myocardium and to a reduction in left ventricular compliance. In response to shock the systemic vasculature responds by vasoconstriction. This increased afterload might further lower stroke volume. In the presence of a grossly raised right atrial pressure caused by right ventricular infarction the formula for calculation of systemic vascular resistance may underestimate the true level of peripheral vascular tone. Right ventricular dilatation may further reduce left ventricular compliance through the constraining influence of the pericardium. This may be worsened by overenthusiastic and possibly ill advised use of fluid infusion. Hypoxia may extend the degree of ischaemic damage to the left ventricle and is a frequent finding in shock caused by right ventricular infarction, even in the absence of pulmonary oedema.[8] Hypoxia will increase peripheral vascular tone and further depress left ventricular function by increasing the afterload.

The improvements in left ventricular performance that were brought about by the use of inotropes in the current study may have been because conditions for their use were optimised by correction of hypoxia, rational use of volume loading or nitrates to produce an optimal preload, and careful titration of the dosage guided by constant clinical and haemodynamic evaluation.

In the present study, reversal of shock was achieved without any increase in right ventricular stroke work index. This suggests that right ventricular dysfunction was not primarily responsible for the state of shock.

Animal experiments showed that complete ablation of the right ventricle had little demonstrable effect on resting venous or arterial pressure; however, volume loading was not used in the early studies.[28 29] These experiments usually involved removal of the restraining influence of the pericardium.

Without additional cardiovascular stress extensive replacement of right ventricular myocardium by fibrous and adipose tissue in the rare Uhl's anomaly can be consistent with adequate haemodynamic function, and it has been suggested that the pulmonary blood flow can be maintained by right atrial contraction.[30]

Some support for our hypothesis comes from a close examination of the results of a previous study of patients in shock. Gewirtz *et al* compared the initial haemodynamic profiles of patients with inferior myocardial infarction who had cardiogenic shock with those without shock.[31] The shock patients were divided into those with and those without right ventricular dysfunction. Though right ventricular stroke work index was reduced in those with right ventricular dysfunction, the presence of shock was associated with a considerable reduction in left ventricular stroke work index in both groups. This showed that left ventricular dysfunction may be more extensive than had been thought. Plasma volume expansion to produce an optimum pulmonary artery occlusion pressure did not improve the overall cardiac index in three of the six patients with shock and right ventricular dysfunction, all of whom died. Three patients survived but two required intra-aortic balloon counterpulsation. The role of reversal of left ventricular dysfunction was not formally documented in Gewirtz *et al*'s study.

In the current study we confirmed the considerable reduction of left as well as right ventricular stroke work indices, but we also showed that reversal of shock was accompanied by an increase in left ventricular stroke work index while right ventricular stroke work index remained unchanged, which suggests that the left ventricular dysfunction was responsible for the shock. In practice, the need to achieve and maintain an optimal left ventricular filling pressure should not be underestimated, but in those patients whose shock is not due to diuretics or vasodilators volume expansion should be controlled for the reasons described above.

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Desirability of immediate surgical standby for coronary angioplasty

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Abstract

***Objective*—To assess the value of emergency surgical standby for percutaneous transluminal coronary angioplasty.**

***Design*—Retrospective review of the major complications of coronary angioplasty in a regional cardiac centre.**

***Setting*—All angioplasties were performed in the cardiac catheterisation laboratory of Wythenshawe Hospital with surgical standby in an adjoining operating theatre.**

***Patients*—1262 vessels were dilated in 1032 patients (mean age 53 years) between 1984 and 1989.**

***Main outcome measures*—In-hospital mortality from emergency surgical revascularisation after angioplasty; the rate of myocardial infarction and overall morbidity.**

***Results*—Coronary angioplasty achieved primary success in 90% of cases. Thirty eight (3·7%) patients (five women (mean age 55·8) and 33 men (mean age 53·0)) were referred for urgent surgical revascularisation—36 direct to operation and two within 24 hours. All patients survived surgery. Five of the 38 had had a previous angioplasty to the same vessel and one had had previous coronary artery grafts. Four of the 38 had an angioplasty for unstable angina. Eighteen had single, 13 double, and seven triple vessel coronary artery disease. The target vessel was the left anterior descending in 25, right coronary artery in nine, circumflex in three, and the left anterior descending and circumflex coronary arteries in one. Five required external cardiac massage on the way to the operating theatre; two of them had a left main stem occlusion. Four internal mammary artery and 60 reversed saphenous vein grafts were implanted (1·6 per patient). Complete revascularisation was achieved in 36 (94·7%) patients. Q wave myocardial infarction occurred in six (15·8%). The final outcome was: none dead, three patients with angina, one late death, one cerebrovascular accident, one late operation for a new left anterior descending lesion, two patients on diuretics with or without an angiotensin converting enzyme inhibitor. One orthotopic transplant was performed in a patient in whom cardiogenic shock developed after the left anterior descending coronary artery became occluded 72 hours after angioplasty.**

***Conclusion*—There was no surgical mortality and low morbidity among patients for whom immediate surgical cover was requested.**

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The level of surgical cover required for coronary angioplasty is widely debated and ranges from a recommendation for full standby to the need only for facilities at a remote site. It is our practice to have a team on standby in an adjoining operating theatre.

Emergency coronary artery bypass surgery for failed angioplasty is required primarily for acute coronary closure in a patient who is a candidate for operation.[1] A report of the American College of Cardiology/American Heart Association Task Force stated that an experienced cardiovascular surgical team should be available within the institution for emergency surgery for all procedures.[2] This is also the view of the Society of Cardiothoracic Surgeons of Great Britain and Ireland and the International Society and Federation of Cardiology.[3] The results of a recent British study suggest that surgical standby at a different site may allow coronary angioplasty to be carried out on "selected" patients.[4]

Patients and methods

All patients undergoing coronary angioplasty at Wythenshawe Hospital between 1984 and 1989 were included in this retrospective study. Angioplasty (1262 vessels in 1032 patients (mean age 53 years)) was performed in one of two cardiac catheterisation laboratories that are adjacent to three operating theatres. All patients were given 300 mg aspirin before the angioplasty, unless this was contraindicated, and 10 000 units of heparin at the start of the procedure followed by 2000 units per hour.[5] Surgical standby was requested for all patients except those who would not benefit from surgery if a major complication of angioplasty occurred such as those undergoing "salvage" angioplasty. "Salvage" angioplasty was performed in patients with severe angina in whom surgery was deemed inappropriate because of one, or more usually a combination, of the following factors: advanced left ventricular dysfunction, distal vessel disease rendering the patient inoperable, advanced age, coincidental medical illness, and previous coronary artery surgery.

To avoid delays in the cardiac surgical programme, the angioplasty was started as a patient in the operating theatre was coming off cardiopulmonary bypass. Patients were referred for emergency surgery when there was occlusion of a major coronary artery accompanied by myocardial ischaemia which could not be relieved by additional dilatation attempts. Perfusion catheters were used when deemed appropriate.[6] Routine operations were postponed only when a patient was referred for emergency coronary artery bypass surgery. In cases of extreme urgency, the surgical team is prepared to operate in the cardiac catheterisation laboratory. Thus these arrangements result in minimal disruption of the cardiac surgical programme.

Results

The primary angioplasty success rate was 90% with a clinical restenosis rate of 21%. Thirty-eight (3·7%) patients (five women (mean age 55·8) and 33 men (mean age 53·0)) were referred for urgent surgical revascularisation after occlusion of a major coronary artery during coronary angioplasty. Thirty six were operated upon immediately and the remaining two within 24 hours. Five patients required external cardiac massage until the sternotomy was performed; two of them had a vessel occlusion extending to the left main stem. The haemodynamic consequences of myocardial ischaemia were such that three of the five patients requiring cardiac massage were revascularised in the cardiac catheterisation laboratory. All 38 patients survived operation.

Five of the patients who had emergency coronary artery bypass grafts had had a previous angioplasty to the same vessel and one had had previous coronary artery grafts. Four of the 38 had angioplasty for unstable angina. Eighteen had single, 13 double, and seven triple vessel coronary artery disease. The vessel damaged at angioplasty was the left anterior descending in 25 (17 dissections and eight occlusions), right coronary artery in nine (six dissections and three occlusions), circumflex in three (two occlusions and one with hindsight was probably due to an air embolism), and left anterior descending and circumflex arteries in one. Four internal mammary artery grafts and 60 reversed saphenous vein grafts were implanted (1·6 per patient). Complete revascularisation was achieved in 36 (94·7%) patients. We do not know the precise interval to revascularisation, but because of the proximity and availability of the surgical team the operation started within 30 minutes of the decision having been made. The operation was performed on the fibrillating heart in nine patients and cardioplegia was used in 29. The mean aortic cross clamping time was 33 minutes. Nine (23·6%) needed inotropic support for weaning from cardiopulmonary bypass and no patient required an intra-aortic balloon. Q wave myocardial infarction with a rise in cardiac enzymes occurred in six (15·8%) patients. One orthotopic transplant was performed in a patient in whom cardiogenic shock with an occluded left anterior descending coronary artery developed 72 hours after angioplasty when the operating theatre was no longer available.

The final outcome was: no deaths; three patients with angina (grade 1–2), one late death, one cerebrovascular accident, one late operation for a new left anterior descending lesion, two patients on diuretics and an angiotensin converting enzyme inhibitor for heart failure (New York Heart Association classes II and III).

A further five patients died without referral for surgery (0·48%): two had undergone a salvage angioplasty for inoperable coronary artery disease, one had a cerebrovascular accident three hours after the angioplasty, and two died suddenly (six hours and 48 hours) after angioplasty because of occlusion (table 1).

Discussion

In 1979, Gruentzig *et al* reported that of their first 50 patients undergoing coronary angio-

Table 1 Details of patients not referred for emergency surgery who died after coronary angioplasty

Age	*Sex*	*Death*	*History*	*Angiographic details*	*Angioplasty and outcome*
68	M	July 1986	Unstable angina one week after inferior myocardial infarction	Good left ventricular function, inferior hypokinesis, occluded right coronary artery, left anterior descending and circumflex arteries severely diseased proximally	Left anterior descending—good result; asystole 6 h later on cardiac care
68	F	Dec 1987	Unstable angina	Left ventricular ejection fraction 15%, inferior akinesis, left anterior descending and circumflex arteries heavily diseased, subtotal right coronary occlusion with collaterals from the left coronary artery	Left anterior descending and circumflex arteries, occlusion of left anterior descending artery, failure to resuscitate
44	M	Jan 1989	Unstable angina	Good left ventricular function, minor inferior hypokinesis, left coronary artery normal with collaterals to an occluded right coronary	Right coronary artery, some clot in artery, remained on heparin, died suddenly 48 hours later, occluded right coronary artery
71	M	Feb 1989	Unstable angina one week after inferior myocardial infarction	Left ventricular ejection fraction 25%, inferior akinesis, occluded right coronary artery with collaterals from a patent left anterior descending, subtotal circumflex occlusion	Circumflex artery; vessel occluded with considerable hypotension, resuscitation failed
65	M	Feb 1989	Stable angina	Good left ventricular function, occluded right coronary artery, subtotal circumflex disease, severe disease of proximal left anterior descending artery	Left anterior descending artery, occluded vessel cleared by intracoronary streptokinase, massive cerebrovascular bleed 3 h later

Table 2 In-hospital results of emergency coronary artery bypass graft (CABG) surgery after failed elective percutaneous transluminal coronary angioplasty (PTCA)

	Total number of PTCAs	*Emergency CABG (%)*	*Q wave myocardial infarction*	*Deaths (%)*
Current report	1032	38 (3·7)	6 (15·8)	0
Atkins and Block[8]	125	11 (8·8)	1 (9·1)	0
Cowley *et al*[9]	3079	202 (6·6)	52 (25·7)	13 (6·4)
Golding *et al*[10]	1831	81 (4·4)	37 (46)	2 (2·5
Killen *et al*[11]	3000	115 (3·8)	50 (43·5)	13 (11·3)
Pelletier *et al*[12]	265	35 (13·2)	3 (8·6)	0
Reul *et al*[13]	518	70 (13·5)	8 (11·4)	4 (5·7)
Talley *et al*[14]	NA	202	54 (27)	5 (2·5)
Bredee *et al*[15]	4142	155 (3·7)	62 (40)	4 (2·6

NA, not available.

plasty, seven (14%) required emergency surgical revascularisation.[7] Since then, several large series have emphasised the role of immediate surgery for major complications of angioplasty. Table 2 shows the in-hospital results of these studies.[8–15] The results of our study are comparable, with a 3·8% rate for emergency surgery and no surgical mortality; 15·8% of patients undergoing emergency surgery developed Q wave myocardial infarctions, but none required postoperative intra-aortic balloon pumping.[16] It has been suggested that modern techniques including perfusion catheters, atherectomy, lasers, stents, intra-aortic balloon pumping, femoro-femoro bypass, and other temporary bypass support may permit stabilisation of patients with acute ischaemia before elective transfer to the theatre.[17] While these techniques may be successful in some patients, experience is limited. Perfusion catheters are ineffective if there is cardiac arrest and the perfusion pressure is low. Intra-aortic balloon pumping can only be used to support the circulation and could not have improved myocardial perfusion in our patients with left main stem occlusion. We believe that insertion of a balloon pump serves only to delay the one measure likely to save the patient's life.

A smaller series from Belfast has been reported in which only off site surgical facilities were available to cover angioplasty complications.[4] Twelve of 444 patients required urgent surgical revascularisation and none of the patients died. The mean time to surgical revascularisation was 268 minutes. The principal cause for delay was the wait for an operating theatre to become available and not the transfer time between hospitals. The potential benefit for patients who were revascularised more than four hours after the coronary occlusion, and the incidence of myocardial infarction and morbidity were not discussed. Another recent series reported a 40% incidence of myocardial infarction in those undergoing emergency surgery after angioplasty with a minimum time to revascularisation on site of 73 minutes.[15] Our five patients who required external cardiac massage could not have survived had immediate surgery not been available. The events that required surgery were unpredictable such as a thrombus in the left main stem and dissection. The patients who required external cardiac massage were not identified at being at a higher risk before angioplasty. We believe that the immediate availability of surgery for most cases of coronary angioplasty was largely responsible for the lack of surgical mortality and low morbidity in our series.

There is concern that disruption of the routine surgical programme by provision of cover for coronary angioplasty might result in more deaths on the surgical waiting list. Our arrangements, however, resulted in the postponement of 38 routine operations out of a total of 5200 operations performed between 1984–9.

It has been suggested that coronary angioplasty with off site surgical back up makes the best of the facilities we have,[18] whereas another view proposes that the cardiologist rather than the sick patient should travel to the surgical centre to perform coronary angioplasty.[19] The underprovision of cardiac surgical facilities in the United Kingdom gives rise to the claim that the risks of coronary angioplasty covered by a distant surgical team are outweighed by the benefits of a shorter time on the waiting list than would be possible if angioplasty could be undertaken only in a surgical centre.[20] While we acknowledge the force of this argument, we believe that expediency should not be confused with ideal practice.

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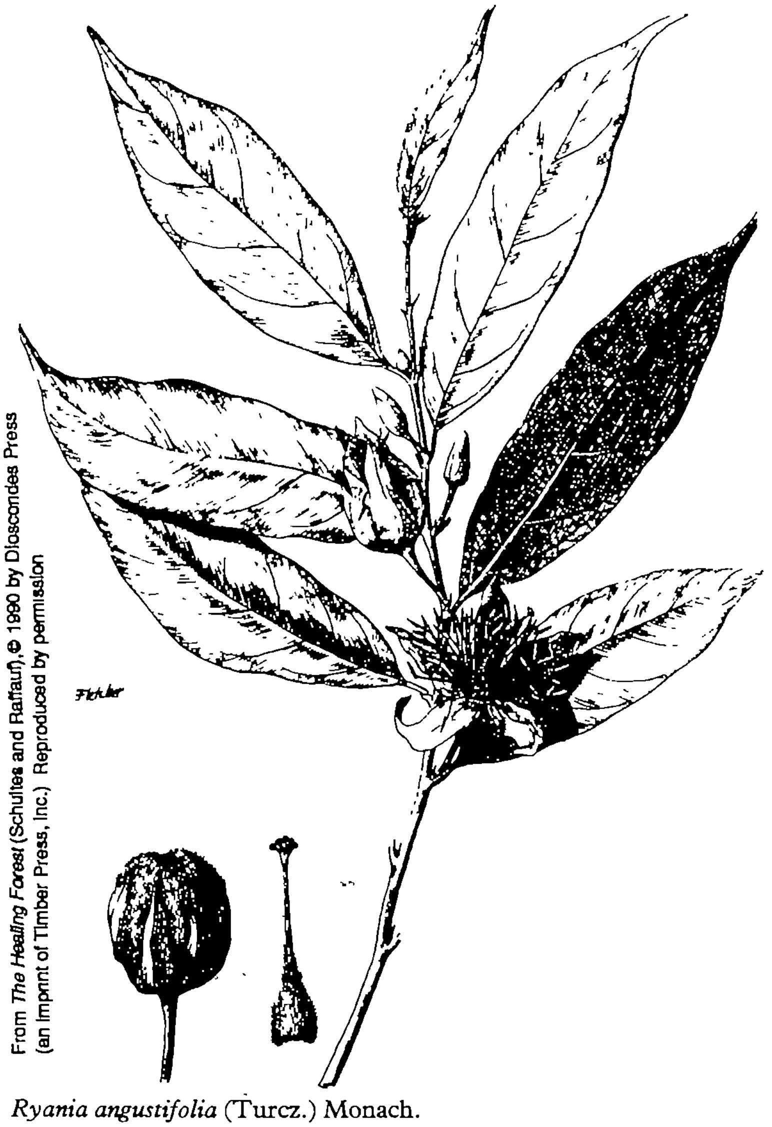
PLANTS IN CARDIOLOGY



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Ryania angustifolia (Turcz.) Monach.

Ryanodine

Ryanodine is a pseudo-alkaloid that is found in *Ryania angustifolia* (Flacourtiaceae) and other species of *Ryania*. It has proved valuable in the study of the calcium release channel of the sarcoplasmic reticulum which it blocks in a dose related manner. Such studies showed that the sarcoplasmic reticulum is a major intracellular calcium store and that it provides most of the energy for cell excitation.

The genus *Ryania* is named after John Ryan, an eighteenth century physician and Fellow of the Royal Society, and its species are small trees in tropical Central and South America. The roots are poisonous and are used to kill rats and alligators, to rid clothing and hair of lice, and even for euthanasia of the elderly by a nomadic Amazonian tribe. Ryanodine was first isolated from *Ryania speciosa* at the Merck Research Laboratories in 1948 during a survey of plant materials for new insecticides.

The family Flacourtiaceae contains a Burmese tree *Hydnocarpus kurzii* whose fruit yields Chaulmoogra oil which was the only effective treatment for leprosy before modern antibacterial drugs. The genus *Idesia* contains salicin, and other genera are used as arrow poisons

A HOLLMAN

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Gradation of unstable angina based on a sensitive immunoassay for serum creatine kinase MB

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Abstract

A newly developed, highly sensitive immunoassay for creatine kinase MB isoenzyme was evaluated in 68 patients with or without different types of ischaemic heart disease. Patients were classified on the basis of clinical criteria in four groups: no ischaemic heart disease, stable angina, unstable angina, and acute myocardial infarction. Enzyme concentration in patients with stable angina was the same (even during exercise) as seen in the patients without ischaemic heart disease. Patients with unstable angina, however, could be divided into two groups. One group showed clear evidence of severe myocardial ischaemia by serial changes and higher mean values of creatine kinase MB up to 40 hours after the onset of symptoms, whereas in the remainder values were stable and resembled those seen in the patients without ischaemic heart disease. The changes in concentration correlated with signs of repetitive ischaemic episodes deduced from continuous ST segment monitoring during the first 24 hours after admission. These findings indicate that patients with unstable angina are a heterogenous group. In some, severe and prolonged ischaemia can be detected by a serological assay with high sensitivity.

Ischaemic heart disease is expressed clinically as stable chronic angina and the acute ischaemic syndromes of unstable angina, acute myocardial infarction, and sudden ischaemic death. Sound clinical and pathological evidence indicates an underlying pathogenesis of chronic static lesions or an acute and evolving process superimposed on atherosclerosis.[1–4] The mechanism that leads to acute ischaemia is uncertain. Thrombosis is a major factor,[1–4] but progression of atherosclerosis and coronary spasm may also be important.[4 5] These conditions can cause myocardial ischaemia, which in cases of myocardial infarction results in cell death and tissue necrosis. In unstable angina, a dynamic stenosis can also cause unpredictable episodes of ischaemia. Such attacks of repeated ischaemia are not detectable by conventional methods such as electrocardiography and immunochemical, chromatographic, or electrophoretic assays for serum creatine kinase isoenzymes, but some studies suggest that they cause a slight release of enzymes.[6 7]

We evaluated a newly developed, highly sensitive immunoassay for the creatine kinase isoenzyme MB in patients with ischaemic heart disease, with a view to classifying their disease on the basis of biochemical evidence of slight myocardial damage.

Patients and methods

PATIENTS

The study population consisted of 68 patients divided into four groups: 23 patients without ischaemic heart disease (group 1); 10 patients with stable angina pectoris (group 2); 21 patients with unstable angina (group 3); and 14 patients with acute myocardial infarction (group 4). The patients without ischaemic heart disease and patients with stable angina attended our outpatient clinic. Patients with stable angina were taking antianginal agents (long acting nitrates, calcium antagonists, or β blockers, or a combination of these drugs). Patients with unstable angina and acute myocardial infarction were recruited after admission to the coronary care unit within 12 hours of the development of retrosternal pain at rest. The mean time from onset of chest pain was 4 h 10 min (range 55 min–10 h 30 min) in patients with unstable angina and 3 h 35 min (range 1 h–10 h 30 min) in patients with acute myocardial infarction.

Eight (38·1%) of the 21 patients with unstable angina had not previously had symptoms of ischaemic heart disease. Thirteen patients (61·9%) had well established ischaemic heart disease—chronic stable angina in 12 (57·1%) and/or previous myocardial infarction in nine (42·9%). Among these, five patients were treated with nitrates, one with a β blocker agent, three with calcium antagonists, and two with a combination of β blockers and calcium antagonists.

Six (46·2%) of the patients with acute myocardial infarction had previously had symptoms of ischaemic heart disease: five had had chronic stable angina and four an earlier myocardial infarct. One patient was treated with nitrates, two patients with calcium antagonists, and two patients with β blockers.

Patients admitted to hospital with unstable angina and acute myocardial infarction were treated with bed rest and control of cardiac pain by nitrates, morphine, and oxygen. No patient had haemodynamic disturbances or arrhythmias that required medical treatment. During the period of blood sampling aspirin treatment was started in all patients. Four patients with acute myocardial infarction started taking diltiazem and five others were treated with intravenous glyceryl trinitrate. All the patients with unstable angina were treated with diltiazem and seven were given intravenous glyceryl trinitrate. A maximum of 480 ml of glyceryl trinitrate was infused in 24 hours. Treatment did not influence the interpretation of the analytical results because in each patient the concentration of serum albumin remained constant within the study period.

Informed consent was obtained from each patient and the study was approved by the regional scientific ethics committee.

DIAGNOSTIC CRITERIA

Group 1 (no ischaemia) comprised patients without a history of chest pain and without electrocardiographic signs of ischaemia both at rest and during exercise. Patients in group 2 (stable angina) had typical attacks of chest pain provoked by physical exertion or psychological factors that were relieved by glyceryl trinitrate. The diagnosis was confirmed by a positive exercise test during which chest pain was provoked along with at least 0·1 mV ST depression. Unstable angina (group 3) was diagnosed on the basis of chest pain at rest or brought on by minimal exertion and/or an entirely new pattern of chest pain in patients previously classified as having chronic angina.[8] ST depression or T wave inversion were not obligatory; none had signs of myocardial infarction. Conventional serum creatine kinase B residual-activity (that is after removal of MM and part of MB) was within normal range (<12 U/l) throughout the period of measurement. The diagnosis of acute myocardial infarction was based on the criteria of the World Health Organisation[9]—that is, characteristic chest pain, unequivocal signs of infarction in the electrocardiogram, and a characteristic increase in enzyme activity of serum creatine kinase B and lactate dehydrogenase.

PROCEDURE

After informed consent was obtained, long acting antianginal medication was stopped a week before the study in the patients with stable angina. The patients without ischaemic disease and with stable angina were exercised on bicycles—until exhaustion in patients without ischaemia and until both pain and ST depression of at least 0·1 mV occurred in patients with stable angina. Blood samples were drawn before and every 3–6 hours up to 24 hours after exercise. Blood samples were drawn from patients with acute myocardial infarction and unstable angina on admission and every 3–6 hours during the first 24 hours and then every eight hours up to 72 hours.

BLOOD SAMPLING

Samples were drawn into tubes without anticoagulant through a catheter permanently placed in an antecubital vein. The samples were stored at +4 C for 15 minutes and then centrifuged at 3000 *g* for 10 minutes. The serum was stored at −21 C until analysis. After thawing the serum was again centrifuged to remove any precipitate.

ANALYTICAL METHODS

The creatine kinase (EC 2.7.3.2) isoenzyme MB was measured by a newly developed and specially designed highly sensitive enzyme labelled immunosorbent assay (NovoClone CK-MB, Novo Biolabs, Cambridge, United Kingdom). Serum samples were simultaneously incubated with CK-B-specific antibodies attached to the polystyrene surface of the wells in a microtitration plate and with CK-M-specific antibodies conjugated with peroxidase. After one hour's incubation the microtitration plate was washed to remove non-adherent components and the remaining peroxidase activity was measured by an end point assay with orthophenyl diamine as the substrate. The incubation time was 15 minutes and the absorbance was read on an Archimedes plate reader (Novo, Copenhagen). We established a calibration curve using samples with concentrations of 1–30 µg/l. All controls, calibration samples, and clinical samples were analysed in quadruplicate and the figures averaged to minimise variability. Specimens containing more than 30 µg of creatine kinase MB per litre were reassayed by the same assay with a wider range of detectability.

In a previous study of 315 outpatients (132 men and 183 women) without myocardial diseases the reference interval was 0–6 µg/l. The overall median of the log gaussian distribution was 1·91 µg/l (2·03 µg/l for men and 1·79 µg/l for women). Total and within assay coefficient of variance was less than 6% at the upper reference limit. The detection limit was 0·1 µg/l.[10]

The serum concentration of the creatine kinase B subunit was measured by an homogeneous enzyme immunoassay after inhibition of creatine kinase M-subunit activity.[11] Correction for residual adenylate kinase was done before we calculated the enzyme concentrations. For a creatine kinase B-subunit activity of 20 U/l the coefficient of variance was 5%.

HOLTER MONITORING

The ST segment was monitored in patients admitted to the coronary care unit with angina at rest. Recordings were taken from an anterior lead (CM5) and an inferior lead on magnetic tapes (Tracker recorder, Reynolds Medical, England). Tapes from patients with unstable angina were analysed for ST segment changes at Reynolds Medical by computer. Significant ST segment depression was defined as a horizontal or downward sloping ST segment shift of >0·1 mV 0·08 s after the J point that persisted for more than 1 minute.

STATISTICAL ANALYSIS

We used Student's *t* test to analyse the significance of difference between means and the F statistic for the significance between the variances. We used Fisher's exact test to measure the significance of association be-

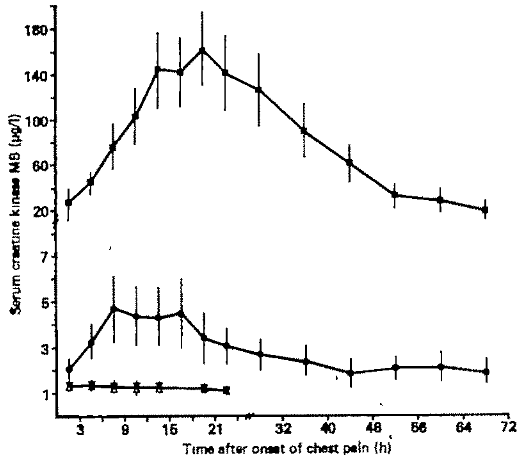

Figure 1 Serum creatine kinase MB concentration (mean (SEM)) in four patient groups measured at three hour intervals in the first 24 hours after exercise (no ischaemic heart disease (△) and stable angina (▼)) and at 3–8 hour intervals in the 72 hours from onset of chest pain (unstable angina (●) and acute myocardial infarction (■)).

tween serum enzyme fluctuation and Holter analysis. p Values of <0.05 were regarded as significant.

Results

PATTERNS OF CREATINE KINASE MB

Figure 1 shows the mean values of serum creatine kinase MB concentration every three hours during the first 24 hours after exercise in the patients without ischaemic disease and in those with stable angina and during the first 72 hours after the onset of chest pain in patients with unstable angina or acute myocardial infarction. Because there was no difference between the mean concentrations of serum creatine kinase MB in patients without ischaemic heart disease and patients with stable angina we considered groups 1 and 2 together. The patients (group 3) with unstable angina had a higher mean concentration than this combination group from 3–6 hours to 21–24 hours ($p < 0.05$). Patients with acute myocardial infarction had significantly higher creatine kinase MB concentration than those with unstable angina from 3–6 hours to 64–72 hours ($p < 0.01$).

To determine whether enzyme release occurs during exercise, serum concentrations of creatine kinase MB were measured before, immediately after, and one hour after an exercise test in patients without ischaemic heart disease and patients with stable angina. These concentrations resembled those measured 3–24 hours after exercise.

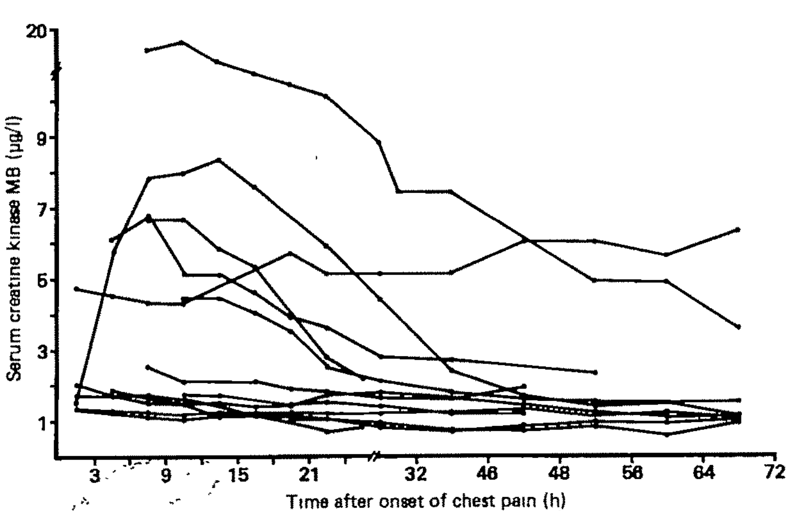

Figure 2 Time course of serum creatine kinase MB concentration in 21 patients with unstable angina measured at 3–8 hour intervals for 72 hours after onset of chest pain.

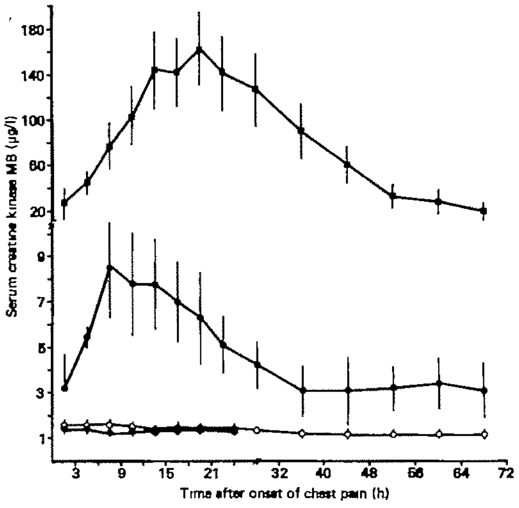

Figure 3 Serum creatine kinase MB concentration (mean (SEM)) in UA (−) (○) and UA (+) (●) patients measured every 3–8 hours in the 72 hours after the onset of chest pain compared with mean concentration in the combined groups of patients without ischaemic heart disease or with stable angina (◆) and patients with acute myocardial infarction (■).

VARIABILITY OF SERUM CREATINE KINASE MB

There was considerable variation in the patients with acute myocardial infarction and in eight (38%) of the patients with unstable angina (fig 2). In the group with unstable angina 13 (62%) patients had almost constant values ($p < 0.01$). The time course of changing enzyme concentrations in seven of the eight patients with enzyme fluctuation was similar to the curves obtained from patients with acute myocardial infarction. One patient had a different time course because the serum concentration of creatine kinase MB increased somewhat throughout the period of investigation. This patient had prolonged periods of chest pain, but did otherwise not differ from the others.

In figure 3 the mean concentrations of serum creatine kinase MB in the eight patients with unstable angina and enzyme changes UA(+) and the 13 patients with unstable angina and no enzyme changes UA(−) are compared with concentrations in the combined group (no ischaemic heart disease + stable angina) and the group with acute myocardial infarction. The UA(+) group had significantly higher mean values than the combined group in the interval from 3–6 hours to 32–40 hours ($p < 0.05$). The UA (−) group did not differ from the combined group. The UAP (+) group had a creatine kinase MB concentration curve that resembled that of the patients with acute myocardial infarction but the concentration was significantly lower in the interval from 3–6 hours to 32–40 hours ($p < 0.05$). There was an earlier peak of serum creatine kinase MB in the UA (+) group than in the patients with acute myocardial infarction.

COMPARISON WITH CREATINE KINASE-B

Figure 4 shows that the mean serum creatine kinase-B residual activity was similar in the UA (+) and UA (−) patients.

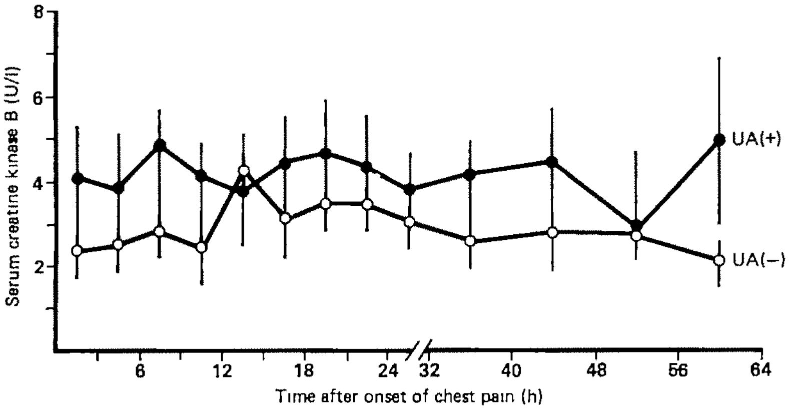

Figure 4 Serum creatine kinase B residual activity (mean (SEM)) in UA (−) and UA (+) groups measured every 3–8 hours in the 72 hours after the onset of chest pain

CREATINE KINASE MB AND ELECTROCARDIOGRAM ON ADMISSION IN PATIENTS WITH UNSTABLE ANGINA

Reversible electrocardiographic changes (ST segment depression or elevation $\geq 0 \cdot 01$ mV or T wave inversion, or both) were found at admission in six (46%) of 13 patients with UA (−) and in seven (88%) of eight patients with UA (+). The difference was not statistically significant ($p = 0 \cdot 27$).

CREATINE KINASE MB AND ST SEGMENT CHANGES IN PATIENTS WITH UNSTABLE ANGINA

Twenty of the 21 patients with unstable angina had ST segment analysis by Holter monitoring during the first 24 hours after admission. There were episodes of significant ST segment depression in six of 12 patients with UA (−) but in all patients with UA (+). There was a significant association between the presence of reversible ST segment depression and serum enzyme fluctuation ($p < 0 \cdot 05$).

CREATINE KINASE MB AND IN-HOSPITAL CLINICAL OUTCOME

The presence of ischaemic heart disease was confirmed by either an exercise test or coronary angiography in all patients with unstable angina. No patients with unstable angina without enzyme changes had coronary events during their hospital stay. Two patients with unstable angina and enzyme changes later had an acute myocardial infarction during their hospital stay.

Discussion

The results of the present study indicate that the new creatine kinase MB immunoassay is a promising diagnostic tool because it may help to determine the frequency and severity of myocardial ischaemic events in the different coronary syndromes. Until now assessment of damage to the ischaemic myocardium by measurement of creatine kinase isoenzymes has mainly been based upon analysis of creatine kinase B by immunochemical methods or creatine kinase MB by electrophoretic or chromatographic methods.[12-14] These methods are satisfactory for diagnosing acute myocardial infarction but they are less sensitive for monitoring continuing myocardial ischaemia. Creatine kinase MB specific enzyme linked immunoadsorbent assays have a high sensitivity.[15-18] This method has been further improved by using a double antibody technique, which gives a highly specific and sensitive assay with a very low limit of detectability.[10]

In the present study the group without ischaemic heart disease represents the background serum concentration of creatine kinase MB and the group with acute myocardial infarction the full extent of enzyme concentration when there is irreversible cell damage. So these two patient groups are ideal reference groups for the study of serum enzyme concentration in patients with angina pectoris.

Despite the fact that ischaemia of short duration, verified electrocardiographically, was induced by exercise serum creatine kinase MB concentrations in the group with stable angina resembled those in the group without ischaemic heart disease This indicates no enzyme leakage after a transient ischaemic attack in patients with chronic stable angina. Similar results have been reported by others.[6 10]

In the group with unstable angina, however, our results indicate that the grade of unstable angina may reflect the degree of myocardial damage. Some of the patients with unstable angina showed clear evidence of ischaemic injury—serial changes and higher mean values of serum creatine kinase MB concentration—after the onset of symptoms than a reference group of patients without ischaemic heart disease or with stable angina. In addition, fluctuations in creatine kinase MB correlated with evidence of repetitive ischaemic episodes on continuous ST segment monitoring during the first 24 hours after admission.

Whether enzyme release is due to minor necrosis of myocardial tissue or severe but reversible ischaemic injury cannot be determined from the present study. Enzyme leakage has been found under experimental conditions in ischaemically damaged myocardial tissue without signs of irreversible myocardial injury.[20 21] On the other hand, studies of patients suggested that slight increases in serum concentrations of creatine kinase and creatine kinase B were caused by micronecroses.[22] This is supported by techniques such as myocardial scintigraphy with technetium-99m-pyrophosphate and necropsy studies.[23 24]

In patients with unstable angina serum creatine kinase MB concentrations were only slightly raised and the time course of the increase in creatine kinase MB resembled the curves obtained from patients with acute myocardial infarction. This suggests that patients with unstable angina had minimal myocardial necrosis. The earlier rise in peak creatine kinase MB in unstable angina resembled the enzyme course described in patients with non-Q wave infarction and has led to the hypothesis that reperfusion is likely to occur in patients with non-Q wave acute myocardial infarction.[25] Reperfusion is also likely to occur after transient non-perfusion in unstable angina. However, the UA (+) patients did not have acute myocardial ischaemia by the classic World Health Organisation criteria.[9] Findings were similar when serum myoglobin was used as a marker of myocardial ischaemia in a group of patients with an acute ischaemic myocardial insult.[26] Therefore the gradation of patients with unstable angina implies the identification of a subgroup with small size myocardial necrosis. The various time courses of creatine kinase MB within this population (fig 2) further indicate that this enzymatic marker of myocardial ischaemia need not be restricted to conventional myocardial infarction. It also reflects—in time and degree—the range of ischaemic damage of myocardial tissue. In this context the present results confirm that myocardial infarction and enzyme release are not all-or-non processes, but rather a continuum dependent on the duration and intensity of ischaemia and on the condition of the myocardium at the onset of the ischaemic episode.[26–28]

The subgrouping of patients in a study of this type is crucial. Unstable angina was diagnosed on clinical grounds and acute myocardial infarction was excluded by conventional enzymatic methods and electrocardiographic findings. Though the term unstable angina includes a wide range of patients with ischaemic heart disease the term has been clinically defined. To improve the understanding of this complex clinical entity, Braunwald recently proposed a clinical classification of unstable angina.[29] This classification is based on the severity of angina—new onset of severe angina or accelerated angina, angina at rest within the past month but not within the preceding 48 hours, and angina at rest within 48 hours. These three grades of severity are classified further on the basis of the development of angina in the presence of extracardiac conditions that intensify myocardial ischaemia, develop in the absence of extracardiac conditions, or develop within two weeks after acute myocardial infarction. According to this classification all patients with unstable angina in the present study had primary unstable angina (group IIIB) because they presented with angina within 48 hours in the absence of extracardiac conditions. Half of a similarly defined group of patients with unstable angina had raised concentrations of serum myoglobin.[26] This accords with our finding raised concentrations of serum creatine kinase MB in 38% of the patients.

Coronary events occurred only in the patients with unstable angina who also had raised serum creatine kinase MB. This increase in serum creatine kinase MB may be an additional prognostic factor in patients with unstable angina. This point adds further support to the view that patients with unstable angina and raised creatine kinase MB activity have areas of myocardial necrosis.

The highly sensitive creatine kinase MB immunoassay is a promising means of extending our knowledge of the severity of myocardial ischaemic events in the different coronary syndromes. Application of the method is not restricted to conventional myocardial infarction. It is able to reflect—in time and degree—the range of ischaemic damage in myocardial tissue. The different time courses of creatine kinase MB in various patient groups in the present study show that the acute ischaemic syndrome—comprising unstable angina, acute myocardial infarction, and sudden ischaemic death—represents a continuum of ischaemic myocardial damage. It is tempting to suggest that the difference between no enzyme release and minimal enzyme release reflects a separation between stable and dynamic ischaemic conditions; if so the "dividing line" would fall within unstable angina.

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Overnight studies in severe chronic left heart failure: arrhythmias and oxygen desaturation

S W Davies, L M John, J A Wedzicha, D P Lipkin

Abstract

Overnight studies were performed in 10 patients with severe chronic left heart failure (New York Heart Association grades III and IV) without pulmonary disease and in eight controls. Transcutaneous oxygen ($P\mathrm{O}_2$) and carbon dioxide tensions ($P\mathrm{CO}_2$) and oxygen saturation were measured and the electrocardiogram was recorded. During sleep mean oxygen saturation fell to 92·7% (minimum 86·1%) from 95·1% when awake. During the night oxygen saturation was below 95% for 62% of the time, below 90% for 6% of the time, and below 85% for 1% of the time. In four patients there were oxygen desaturation dips (a fall of > 4% in oxygen saturation from a stable baseline that lasted > 30 s) with concurrent increases in $P\mathrm{CO}_2$. Two patients had bradycardia during the dips: in one there was non-sustained ventricular tachycardia during the dips and in the other there was ST depression (> 0·1 mV at 80 ms after the J point) during a dip. In the controls the fall in mean oxygen saturation from 95·4% when they were awake to 94·4% when they were asleep was less than the fall in patients with heart failure and there were no desaturation dips or arrhythmias.

Thus patients with severe heart failure had episodes of oxygen desaturation during sleep, some of which were associated with arrhythmia. Such episodes may be related to the increased risk of sudden death in chronic heart failure.

The prognosis in patients with severe chronic left heart failure (New York Heart Association grades III and IV) is poor, with a mortality of 40–50% at 12 months.[1-3] Between one third and one half of these deaths are sudden,[1-3] and this is true both of patients with end stage ischaemic heart disease and those with idiopathic dilated cardiomyopathy.[1 4] Whatever the aetiology, many deaths in patients with severely impaired left ventricular function are sudden.

The pathophysiology of sudden death in severe chronic left heart failure is not known, but some or all of these deaths may be related to dangerous ventricular arrhythmias.[5] Twenty four hour monitoring of the electrocardiogram showed frequent ventricular arrhythmias in such patients,[6-8] and electrophysiological testing showed a low threshold for ventricular arrhythmias.[9] Factors that might trigger such arrhythmias during everyday life have not been fully defined, however.

Patients with severe chronic airflow obstruction had episodes of arterial oxygen desaturation during sleep[10 11] that were associated with profound haemodynamic disturbance and arrhythmias.[12 13] Similar episodes might act as triggers for ventricular arrhythmias in chronic heart failure. We therefore performed overnight sleep studies in patients with chronic severe left heart failure to determine the presence of such episodes and their possible relation to arrhythmias.

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Patients and methods

PATIENT SELECTION

Overnight studies were performed on 10 patients (eight men and two women, aged 33–76) with severe chronic left ventricular impairment and New York Heart Association grade III or grade IV dyspnoea. All were treated with diuretics (frusemide 80–160 mg/day or its equivalent) and angiotensin converting enzyme inhibitors. All were clinically stable at the time of the study, without radiographic pulmonary oedema; four patients were on the waiting list for cardiac transplantation. The left ventricular ejection fraction determined by gated blood pool scanning was < 40% in all cases. Only one of the patients gave a history suggestive of sleep disordered breathing (snoring, daytime somnolence, and morning headache). None of the patients took sedatives at night.

We excluded patients with (*a*) evidence of important intrinsic pulmonary disease, as judged by history and clinical examination, normal peripheral lung fields on chest *x* ray, and standard lung function tests (forced expiratory volume in one second, forced vital capacity, and carbon monoxide diffusing capacity) > 75% of predicted normal values; (*b*) current treatment with antiarrhythmic drugs; and (*c*) known ear, nose, or throat disease, or obesity (> 115% ideal body weight). For comparison control data were obtained from eight healthy individuals (ages 32–75) referred to the sleep laboratory for investigation of possible sleep disordered breathing. All the controls had normal lung function and normal cardiac function (clinical examination, electrocardiogram, chest *x* ray, lung function tests, echocardiogram). None of them had sleep disordered breathing on overnight study.

OVERNIGHT STUDIES

All those with chronic heart failure were inpatients undergoing assessment of heart failure at the time of the overnight study. Studies were performed at the bedside in the hospital ward on the third to eighth night after admission. Patients were thus familiar with the room and environment before the night on which the recordings were made. The following measurements were made: (*a*) transcutaneous oxygen tension (Po_2) by a Radiometer TCM2 electrode applied to anterior abdominal wall; (*b*) transcutaneous carbon dioxide tension (Pco_2) by a Radiometer TCM20 electrode applied to anterior abdominal wall; (*c*) oxygen saturation and heart rate from an Ohmeda Biox III pulse oximeter applied to a finger. The output from these devices was recorded on a four channel paper chart recorder (Honeywell Analogic).

Raw values of Po_2 and Pco_2 from the electrodes were corrected by a standard empirical formula validated for this laboratory. This standardisation was checked in each subject by comparing the values of transcutaneous Po_2 and Pco_2 with arterialised capillary blood samples from the ear lobe[14] analysed in a Radiometer ABL3 machine at the start of the overnight study.

Heart rate, rhythm, and ST segment changes were recorded by a two channel Holter monitor with a wide band pass (Oxford Medilog mark II). The frequency response of 0·05–100 Hz meets American Heart Association specifications,[15] and units were calibrated both before and after placement. Channel I recorded the lead with a configuration resembling that of precordial lead V5, and channel II recorded a lead with a configuration resembling that of standard lead III. Important ischaemic episodes were defined as transient ST segment depression > 0·1 mV from the baseline at 80 ms after the J point, lasting for at least one minute.[16] Each episode was confirmed by direct examination of the ST segments before, during, and after the episode on a full disclosure electrocardiogram. An interval of at least two minutes of normal tracing was required after resolution of each episode before another discrete episode was counted.[16]

We recorded synchronous time markers at the start and end of each study by the event marker channels of the Holter monitor and of the respiratory monitor to ensure accurate correlation between the two recordings. The accuracy of the time markers was confirmed by comparing heart rate changes on the electrocardiogram with those recorded on the paper chart recorder by the pulse oximeter.

DATA ANALYSIS

Overnight recordings of Po_2, Pco_2, and oxygen saturation were read by two experienced observers independently. Dips in oxygen saturation were defined as an abrupt fall in oxygen saturation by at least 4%, lasting for at least 30 seconds.[17,18] We used standard criteria to identify episodes of ST segment depression, as given above. A significant episode of bradycardia was defined as a fall in mean heart rate by at least 10 beats per minute, so that the absolute heart rate fell below 60 beats per minute, lasting for at least 30 seconds.

STATISTICAL ANALYSIS

Values of variables are given as range and median; we used the appropriate non-parametric statistical tests in analyses. The group of patients with heart failure and the control group were compared by the Mann-Whitney U statistic for continuous variables and Fisher's exact test for categorical variables. We used the Wilcoxon matched pairs signed rank test to compare measurements made when the patients were awake with those made when they were asleep.

Results

BLOOD GASES IN CHRONIC HEART FAILURE

At rest all patients with severe chronic left heart failure had normal lung volumes and gas transfer measurements and normal blood gases determined from arterialised capillary samples from the ear lobe (table). Mean oxygen saturation fell significantly from 95·1% (range 93·2–97·0%) when they were awake to 92·7% (89·1–94·8%) when they were asleep ($p < 0·001$). The minimum oxygen saturation during the overnight study in each patient was 86·1% (79·9–90·3%). During the night arterial oxygen saturation was below 95% for 62% (range 40–98%) of the time, below 90% for 6% (1–18%) of the time, and below 85% for 1% (0–5%) of the time. Mean carbon dioxide (Pco_2) rose from 34·1 (29·7–41·9) mm Hg when patients were awake to 37·9 (33·7–45·7) mm Hg when they were asleep ($p < 0·005$).

In four patients there were significant dips with concurrent increases in Pco_2. The number of overnight dips in each individual patient varied from two to eight (mean four). The duration of the dips ranged from one to four minutes. There were clusters of dips in two patients (fig 1).

Oscillations in oxygen saturation were recorded in two patients with chronic heart failure (fig 2). These had a frequency of between 0·45 and 0·8 cycles per minute, and episodes lasted between four and 17 minutes. There were synchronous but opposite changes in transcutaneous Pco_2 consistent with cyclical changes in the depth of ventilation.

ELECTROCARDIOGRAM IN CHRONIC HEART FAILURE

The resting electrocardiogram was abnormal in all patients; all of them had anterior or inferior

Pulmonary function, body weight, and blood gases at rest (range (median)) in patients with severe chronic left heart failure and in controls

	Chronic left heart failure (n = 10)	*Controls (n = 8)*
Age	33–76 (58)	32–75 (56)
Weight (kg)	58–84 (73)	62–91 (74)
FEV_1 (l)	1·7–3·2 (2·4)	2·0–4·8 (3·3)
(as % of predicted)	76–113 (84)	80–125 (98)
FVC (l)	2·1–4·7 (3·1)	3·5–5·5 (4·7)
(as % of predicted)	75–113 (81)	82–119 (96)
Pao_2 (mm Hg)	68·2–89·6 (79·3)	72·9–89·7 (82·6)
$Paco_2$ (mm Hg)	29·7–41·9 (34·1)	33·1–40·6 (36·0)

FEV_1, forced expiratory volume in one second, FVC = forced vital capacity, Pao_2, partial pressure of oxygen in arterial blood; $Paco_2$, partial pressure of carbon dioxide in arterial blood

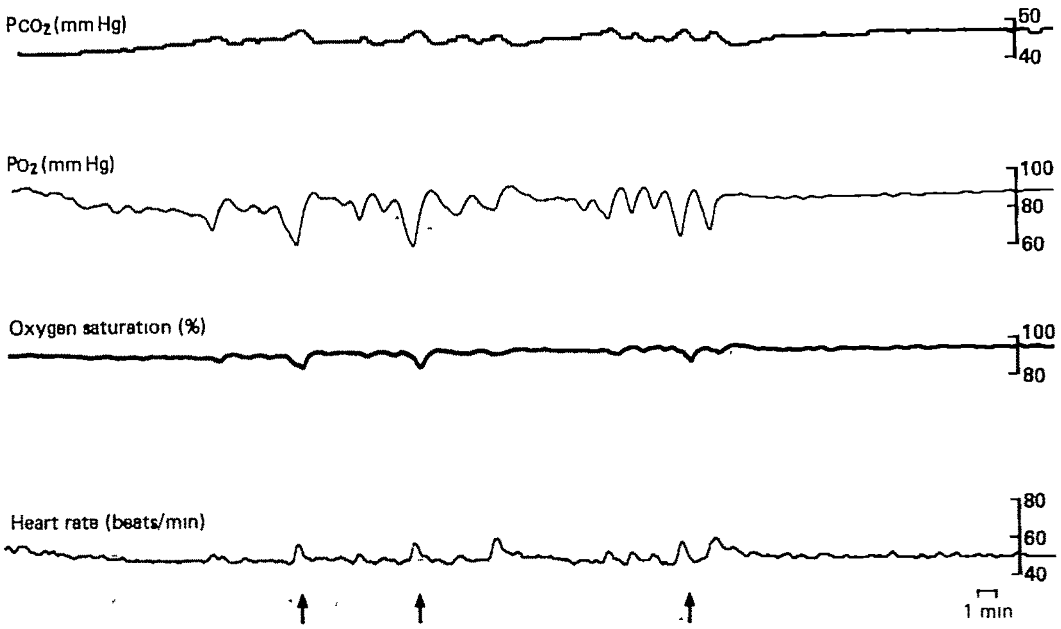

Figure 1 An example of clustering of desaturation dips in a patient with chronic heart failure.

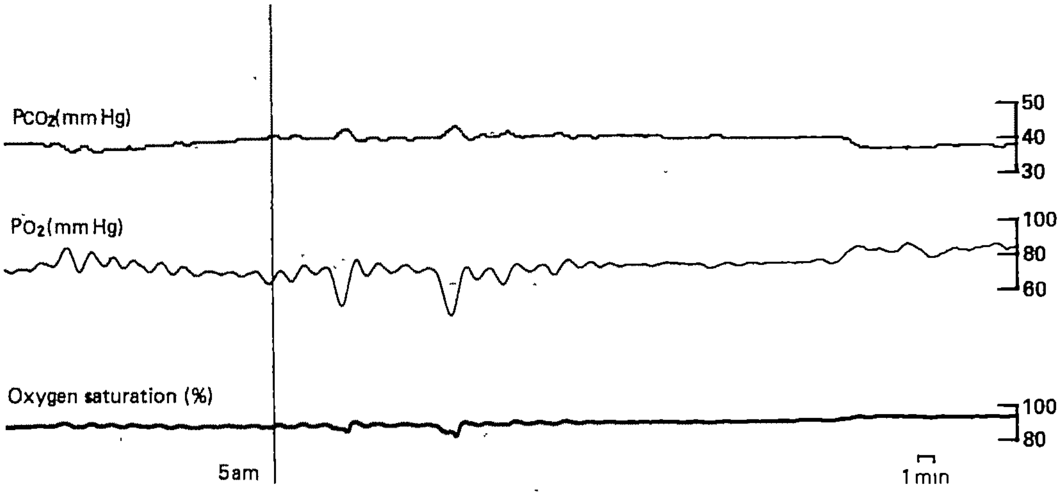

Figure 2 Episode of oscillation in oxygen saturation and carbon dioxide in a patient with chronic heart failure.

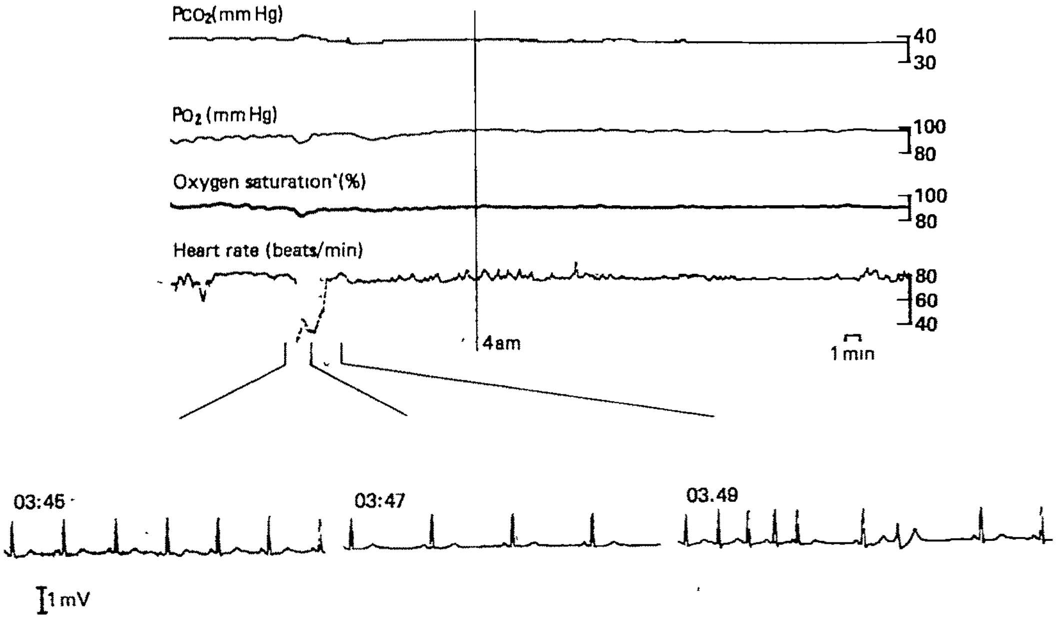

Figure 3 Desaturation dip with associated episode of bradycardia in a patient with chronic heart failure.

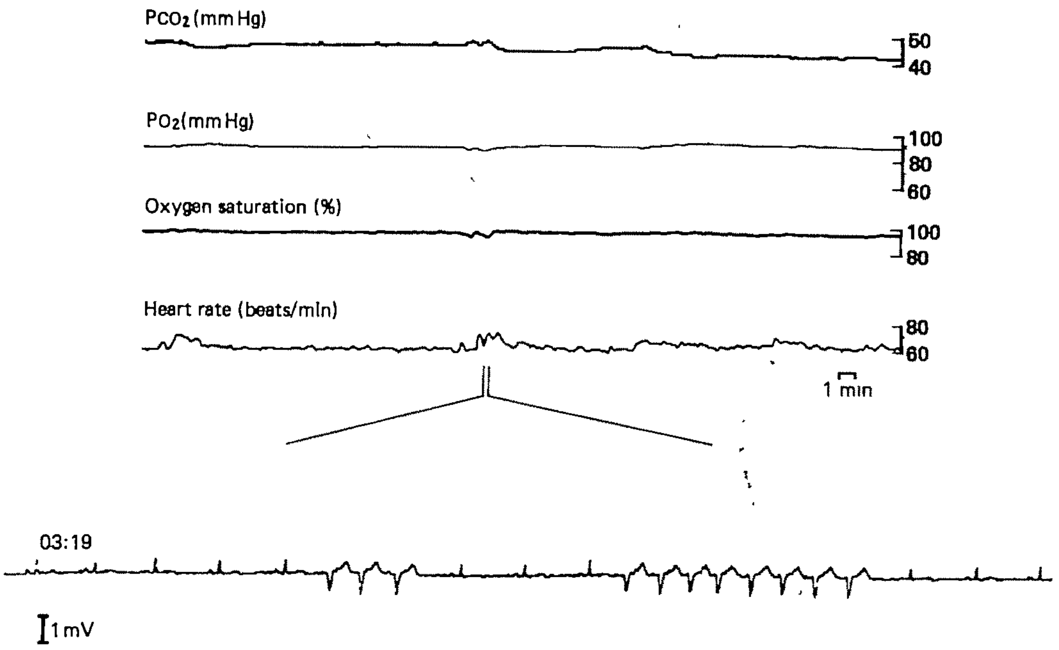

Figure 4 Desaturation dip with associated episodes of non-sustained ventricular tachycardia in a patient with chronic heart failure.

Q wave infarction. ST segments were isoelectric on the resting 12 lead electrocardiogram. During sleep the mean heart rate decreased to 66 (10) bests per minute from 75 (8) beats per minute when patients were awake ($p < 0·005$).

In the six patients without arterial oxygen dips there were no arrhythmias apart from infrequent ventricular extrasystoles (more than three per minute). In two patients with desaturation dips there was transient bradycardia associated with the dips (fig 3). These were confirmed on both Holter monitoring and on the mean heart rate signal from the pulse oximeter. In one patient there were frequent ventricular extrasystoles and short runs of non-sustained ventricular tachycardia during dips (fig 4). No episodes of ventricular tachycardia were recorded in that patient at other times, nor in any other patient. In one patient there was significant ST segment depression during one desaturation dip (fig 5).

The exact time relation of dip and arrhythmia is uncertain because the recordings were made on two separate systems. Synchronous time marks were placed on both recording systems at the start and at the end of each overnight study, and figures 3 and 4 show that the electrocardiographic changes in heart rate mirrored those recorded by the pulse oximeter during the dip. Heart rate during dips started to change within 30 seconds either side of the onset of the dip in oxygen saturation. Transient ST segment depression associated with one dip in a patient also coincided (within 30 seconds) with the onset of the dip.

CONTROL GROUP

Oxygen saturation while the eight age matched

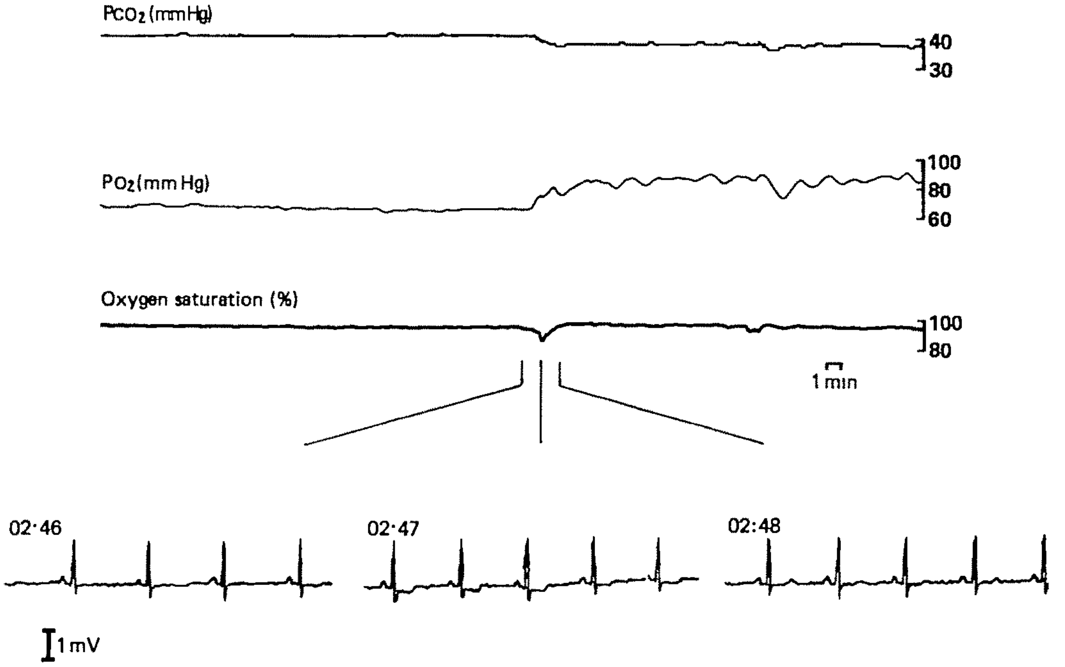

Figure 5 Desaturation dip with associated episode of transient ST segment depression in a patient with chronic heart failure.

controls were awake was similar to that in the patients with heart failure. The fall in mean oxygen saturation overnight from 95·4% (range 93·5–97·2%) to 94·4% (92·4–96·5%), however, was less than in the patients with chronic heart failure ($p < 0·01$). There were no significant desaturation dips and no rhythm disturbances or shifts in ST segment.

Discussion

This study showed that the nocturnal decrease in arterial oxygen saturation and increase in $P\text{CO}_2$ were greater in patients with severe chronic left heart failure than in controls. In some patients with heart failure there were abrupt dips in oxygen saturation, some of which were associated with arrhythmias or episodes of ST segment depression, or both.

The occurrence of sleep disordered breathing in severe chronic heart failure has not previously been defined. We did not deliberately select patients with chronic heart failure and symptoms of sleep disordered breathing and we excluded conditions that might contribute to sleep disordered breathing (pulmonary disease, obesity, nasopharyngeal conditions). Our results suggest that sleep disordered breathing may be common in patients with severe chronic heart failure.

SLEEP DISORDERED BREATHING

Changes in the respiratory pattern and in blood gas tensions during sleep were first recognised in patients with hypoxic lung disease.[10 11] Episodes of arterial oxygen desaturation ("dips") in patients with chronic obstructive airways disease are associated with profound haemodynamic changes,[12 13] and may lead to sustained pulmonary hypertension, secondary polycythaemia, cor pulmonale, and impairment of the central nervous system.[19 20] They may also indicate a poor prognosis.[21] Sleep disordered breathing was also reported in patients with disorders of the upper airways, neuromuscular problems, obesity, and in some apparently healthy normal individuals.[22]

Two distinct mechanisms of apnoea account for the episodes of arterial oxygen desaturation.[22] In central sleep apnoea, airflow at the nose and at the mouth stops for at least 10 seconds and there is a considerable reduction in respiratory movement. In obstructive sleep apnoea, airflow at the nose and mouth stops for at least 10 seconds and this is associated with increased respiratory effort and paradoxical movement of the chest wall. A mixture of both patterns may occur in an individual patient and there may also be episodes of hypopnoea that do not last for at least 10 seconds.

OVERNIGHT ARTERIAL OXYGEN DESATURATION IN CHRONIC LEFT HEART FAILURE

In the present study there was a small but significant fall in mean oxygen saturation during sleep in the patients with chronic heart failure and this was greater than was seen in the control group. The concomitant small rise in $P\text{CO}_2$ suggests this was the result of a minor reduction in alveolar ventilation rather than shunting causing a venous admixture.

Significant desaturation dips with accompanying rises in $P\text{CO}_2$ were seen in four of the 10 patients with severe chronic left heart failure and in none of the eight controls. There are several possible mechanisms for this in the patients with heart failure. Impaired cerebral perfusion and perhaps cerebral hypoxia might lead to central sleep apnoea.[23] Decreased pharyngeal tone as a result of abnormalities of skeletal muscle[24 25] might cause intermittent obstruction of the upper airway. Further studies with full sleep staging are required to distinguish between these possibilities and to elucidate the mechanism of desaturation dips in chronic heart failure. The stage and depth of sleep may be important: in healthy adults ventilation and the ventilatory responses to hypoxia and hypocapnia are smaller during sleep than wakefulness, and are further reduced in rapid eye movement sleep.[26 27] Postural changes in the pulmonary ventilation-perfusion relations in recumbent individuals may also contribute to nocturnal desaturation.[28]

In two patients we found episodes of oscillation in oxygen saturation with synchronous opposite changes in $P\text{CO}_2$. This was consistent with Cheyne-Stokes breathing, which has been described in severe heart failure with low output states.[29] The oscillation may be the result of low cardiac output increasing the transit time from the pulmonary capillary bed to the carotid body and brain stem receptor and introducing a delay into the negative feedback system.[30 31] Reductions in cardiac output during sleep might therefore be responsible for the cyclical oxygen saturation and $P\text{CO}_2$ changes in the two patients in the present study.

ARRHYTHMIAS

In four of the 10 patients with severe chronic heart failure the overnight studies showed important arrhythmias including transient bradycardias, frequent ventricular extrasystoles and brief runs of ventricular tachycardia, and a transient left bundle branch block pattern. No rhythm disturbances were seen in any of the eight controls.

Both bradycardia and tachycardia were associated with oxygen desaturation dips, and often started within 30 seconds of the onset of a dip. Though the changes in oxygen saturation seen in this study were small, they could have acted synergistically with other factors to cause arrhythmias. In severe chronic left heart failure the threshold of the left ventricle to arrhythmia provoked by electrophysiological testing is low.[9] Conversely, it is possible that changes in cardiac output caused by the rhythm disturbance or myocardial ischaemia reduced cerebral perfusion and led to a change in respiratory pattern and to transient hypoventilation. Finally, a transient disturbance of brain stem function might affect autonomic outflow and hence rhythm while simultaneously affecting the respiratory centres and hence the ventilatory drive. There is insufficient evidence to decide between these possibilities, and we cannot at present assign a causal role to the oxygen saturation dips in triggering the arrhythmias we saw.

CLINICAL IMPLICATIONS

Sleep disordered breathing is thought to affect the quality of life of patients with chronic airflow obstruction by disrupting the normal temporal structure of sleep and by contributing to specific symptoms such as nocturnal dyspnoea, general fatigue, malaise, and irritability. The same may apply to patients with severe heart failure. We can also speculate that the cumulative effects of repeated small oxygen saturation dips might in the long term influence myocardial and cerebral function. Though the dips and the overall nocturnal decrease in mean oxygen saturation in heart failure are smaller than in patients with respiratory disorders[10 11] the failing heart may be more sensitive to oxygen desaturation.

Because the occurrence of arrhythmias during everyday life may predict a poor prognosis in chronic heart failure,[32] the association between oxygen saturation dips and arrhythmias (and in one case significant ST segment depression) is of interest. Nobody knows whether the dips in oxygen saturation are causally related to arrhythmias and ischaemia or whether they both reflect brainstem hypoperfusion and autonomic instability. Further study of these dips may provide insight into the mechanisms of sudden death in chronic heart failure. Though the definition of sudden cardiac death in surveys is arbitrary,[33 34] it does include deaths without any antecedent deterioration of cardiac function which are thought to be the result of arrhythmia. The factors that trigger arrhythmias in severe chronic heart failure have not been fully defined, but small changes in oxygen saturation might contribute.

There are circadian rhythms in the time of onset of myocardial infarction[35] and sudden cardiac death.[36] No such pattern has yet been described for sudden death in severe heart failure, but the present findings suggest a mechanism for an excess of nocturnal deaths. This would differ in mechanism and in timing from the early morning peak in myocardial infarction that parallels the normal physiological rhythms of blood pressure, platelet aggregability, fibrinogen concentrations, and plasma catecholamines.[35 36]

Various treatments have been tried for the different forms of sleep disordered breathing. Reducing alcohol intake, withholding hypnotic and sedative drugs, and weight reduction for the obese patient have proved beneficial in selected cases. There is a single case report of sleep disordered breathing in a patient with severe chronic heart failure that resolved when the chronic heart failure was controlled by intensive diuretic treatment.[37] It is too early to advocate more specific treatment for sleep disordered breathing in patients with chronic heart failure. Two recent studies report the apparent benefits of supplemental oxygen[38] and of nasal continuous positive airway pressure[39] in patients with chronic heart failure and overt Cheyne-Stokes respiration.

CONCLUSION

In a group of 10 patients with severe chronic left ventricular failure (chronic heart failure) the decrease in mean arterial oxygen saturation and increase in Pco_2 were both slightly greater than in a control group of eight subjects. In four of the 10 patients with chronic heart failure there were abrupt dips in oxygen saturation during sleep, some of which coincided with arrhythmias or transient ST segment depression or both. The significance of these abnormalities has yet to be evaluated. They may contribute to various symptoms and to the high risk of sudden death in patients with chronic heart failure. Patients with severe heart failure are potentially at risk of arterial oxygen desaturation and may require overnight oximetry to define the degree of respiratory, sleep, and rhythm disturbance.

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Heart rate variability and cardiac autonomic function in men with chronic alcohol dependence

Simon C Malpas, Edwin A Whiteside, Timothy J B Maling

Abstract

Cardiac autonomic function was studied in 23 alcohol dependent men by standard tests of autonomic function and measurement of 24 hour heart rate variability. In all there was peripheral or central nervous system damage or both. Standard tests of autonomic function showed vagal neuropathy in seven. The remainder had normal autonomic function tests. Twenty four hour heart rate variability was measured as the standard deviation of the successive differences between RR intervals from an ambulatory electrocardiogram recording. Twenty four hour heart rate variability was significantly lower in both alcohol dependent groups than in controls, but the results in the two alcohol dependent groups were not significantly different from each other. The results of standard tests of autonomic function did not distinguish between the alcohol dependent men with normal autonomic function and controls. The differences in heart rate variability between this group and the controls may have been the result of the ability of this method to detect small changes in autonomic integrity. Cardiomyopathy may also account for some of these differences and such abnormalities should be excluded before results are to be regarded as a reflection of vagal function. Twenty four hour measurement of heart rate variability may be a more useful index of cardiac vagal neuropathy than currently available tests of autonomic function.

Damage to the autonomic nervous system affecting sudomotor, vasomotor, and cardiac function is a recognised feature of chronic alcohol dependence.[1] Duncan *et al* indicated that vagal neuropathy is a common finding associated with impairment of the central and peripheral nervous systems.[2] Sympathetic dysfunction affecting the control of blood pressure is, however, rare,[3] though orthostatic hypotension may occur in a few patients and is associated with severe autonomic degeneration.[4]

Commonly applied tests of cardiac autonomic function (Valsalva's manoeuvre, deep breathing, and standing) examine heart rate responses to various manoeuvres that change the length of the cardiac cycle (RR interval) over a short period. The change in the RR interval is assumed to be due to autonomic activity but this does not take into account that inputs of different frequencies produce the change in heart rate; those at lower frequencies are not necessarily autonomic in origin such as reflex mechanisms involved with continuing haemodynamic changes. Tests of autonomic function also tend to classify patients merely on the basis of the presence of neuropathy and give little scope for grading its severity.[5] Measurement of short term (5 min) heart rate variability has been advocated as an indicator of autonomic neuropathy[6]; however, there is disagreement about whether the recording should be performed with the patient standing, sitting, or lying and about the best index for measuring heart rate variability.[7] Ambulatory electrocardiographic (Holter) monitoring of heart rate variability may provide a more sensitive index of autonomic function than is currently available[8] because it makes a large number of RR intervals available for the calculation of heart rate variability. Monitoring over 24 hours also provides an opportunity to examine autonomic function during normal daily activities without interference from investigators. It may enable disease progression in alcohol dependent patients to be monitored. Ewing and colleagues reported that heart rate variability was reduced in diabetic patients who had normal standard autonomic function tests.[8] The present study was conducted to test whether similar results apply to alcohol dependent patients and whether 24 hour measurement of heart rate variability is a useful method for assessing cardiac autonomic changes in alcohol dependent patients.

Patients and methods

We assessed autonomic integrity by standard tests of autonomic function and measurement of 24 hour heart rate variability in 23 alcohol dependent men (aged 37–72 (mean 54)) who had been drinking between 100 and 350 g of ethanol daily for 10–40 years. At the time of study all these men were undergoing rehabilitation at a Salvation Army hostel. They were not admitted to hospital for the study. They had abstained from alcohol for one to nine weeks (mean three). None of them had hypertension, diabetes, or clinical evidence of heart disease or were experiencing withdrawal symptoms at the time of study. An electrocardiogram was taken to exclude men with cardiac rhythm abnormalities. Men were selected on the basis of abnormalities of the peripheral and central nervous system by a

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previously described protocol from our laboratory.[2] We also assessed 11 healthy men (aged 34–68). The protocol was approved by the Wellington Hospital Board Ethical Committee and all participants gave their informed consent before taking part.

STANDARD TESTS OF AUTONOMIC FUNCTION

All subjects underwent the following tests of autonomic function in the order below. They lay supine for 20 minutes before the start of the tests. The methods are described elsewhere.[2]

Deep breathing—Sinus arrhythmia of <15 beat/min was regarded as abnormal.

Standing—The 30:15 ratio of the response of heart rate to standing was measured; a ratio $<1{\cdot}03$ was defined as abnormal. The change in blood pressure upon standing was also measured, and a fall >10 mm Hg diastolic and >20 mm Hg systolic indicated sympathetic failure.

Valsalva manoeuvre—Subjects held a forced expiratory pressure of 40 mm Hg for 15 s. The Valsalva ratio of the smallest heart beat interval during straining to the longest after the release of pressure was calculated. A ratio $<1{\cdot}21$ was defined as abnormal.

Neck suction—The carotid baroreceptors were stimulated by the application of suction (-50 mm Hg) to the neck.[9] The suction was applied rapidly (-600 mm Hg/s) and held for 3 s. The longest RR interval during the suction was measured. Failure to prolong the RR interval by >120 ms was defined as abnormal.

Abnormal responses to two or more tests of autonomic function indicated autonomic neuropathy.[10]

MEASUREMENT OF 24 HOUR HEART RATE VARIABILITY

The men were fitted with a Holter monitor (Oxford Medilog, MR14) that recorded two channels of electrocardiogram on to a standard 60 minute cassette tape over a 24 hour period. They kept a self-recorded diary of the day's events such as meal times, exercise, and sleep. Tapes were played back through an analyser (Oxford Medilog, MA14) at 60 times the recorded speed. Fluctuations in the recording speed were adjusted by a phase-locked loop time signal. The QRS waveform was filtered, detected electronically, and a pulse was generated corresponding to each R wave. False triggering of the T wave was inhibited by generating a relatively long width (250 ms real time) for the resultant pulse. The time between R waves was counted by a purpose-built rate logging device (accuracy ± 5 μs) and the data were relayed through a parallel interface to a personal computer (IBM) where the RR intervals were added sequentially to a file. The file containing the RR intervals was divided into sections of 30 minutes of real time RR intervals so that up to 48 subfiles were produced for each 24 hour recording. To eliminate failure of QRS detection, intervals outside a preset range (300 to 1800 ms) and those tapes with more than five extrasystoles per hour were discarded from further analysis.

STATISTICAL ANALYSIS

The alcohol dependent men were divided into two groups on the basis of the presence or absence of autonomic neuropathy as defined by the results of the standard tests of autonomic function. Heart rate variability was assessed from the standard deviation of the successive differences between RR intervals (SDSD) for each 30 min subfile in each individual by a commercial statistical package (SAS Institute, USA) on a Digital Microvax computer. Six controls repeated the ambulatory monitoring between 1–12 weeks later (mean 3). The reproducibility coefficient for the SDSD was 0·83; therefore the method was repeatable.[11] Results from individuals were standardised to a starting time of 0900 h. Two way analysis of variance was used to compare the results of 24 h heart rate variability in controls and the two alcohol dependent groups by a Bonferroni multiple comparisons procedure. The sample size studied had sufficient power, at the 5% level, to detect a change of $>15\%$ in heart rate variability between groups. Results are presented as means (SEM). Statistical significance was achieved when $p<0{\cdot}05$.

Results

STANDARD AUTONOMIC FUNCTION TESTS

Sixteen alcohol dependent men (group 1) had normal standard autonomic function tests. Vagal neuropathy was detected in seven (group 2). Mean responses to standing, Valsalva's manoeuvre, deep breathing, and neck suction were significantly different in group 2 and controls but not between group 1 and controls (table 1). None of the men had sympathetic neuropathy (orthostatic hypotension). There was no difference in age or duration of alcohol dependency between the two groups; however, the degree of peripheral neuropathy, or central nervous system impairment, or both was significantly greater in group 2.

TWENTY FOUR HOUR HEART RATE VARIABILITY

Examination of the diary cards indicated that the alcohol dependent men were generally no more sedentary than the controls and that their times of meals and sleep periods did not differ greatly. All groups showed considerable circadian variation in RR intervals with the slowest heart rate at 0500 h in the controls and group 2 and at 0600 h in group 1. There was a tendency for both alcohol dependent groups to have higher heart rates throughout the 24 h period ($p = 0{\cdot}067$) than the normal group. The

Table 1 Autonomic function test results from 11 controls, 16 alcohol dependent men without vagal neuropathy (group 1) and seven alcohol dependent men with vagal neuropathy (group 2) (mean (SEM))

	Controls	*Group 1*	*Group 2*
Standing (30:15 ratio)	1·12 (0·02)	1·08 (0·03)	1·03 (0·02)
Valsalva ratio	1·74 (0·09)	1·60 (0·11)	1·28 (0·06)
Deep breathing (beats/min)	20 (2·2)	23 (4·4)	7·8 (1·9)
Bradycardia with neck suction (ms)	222 (46)	245 (47)	42 (14)*

*$p < 0{\cdot}05$.

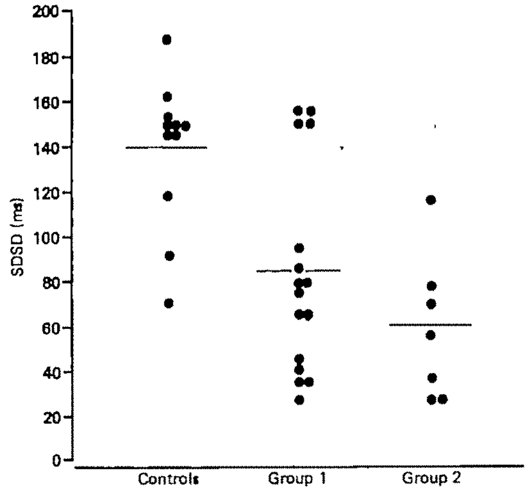

Figure 1 RR intervals and mean heart rate variability (SDSD) over 24 h in 11 controls, 16 group 1 and seven group 2. There was a significant difference in heart rate variability between the alcohol dependent groups and the controls.

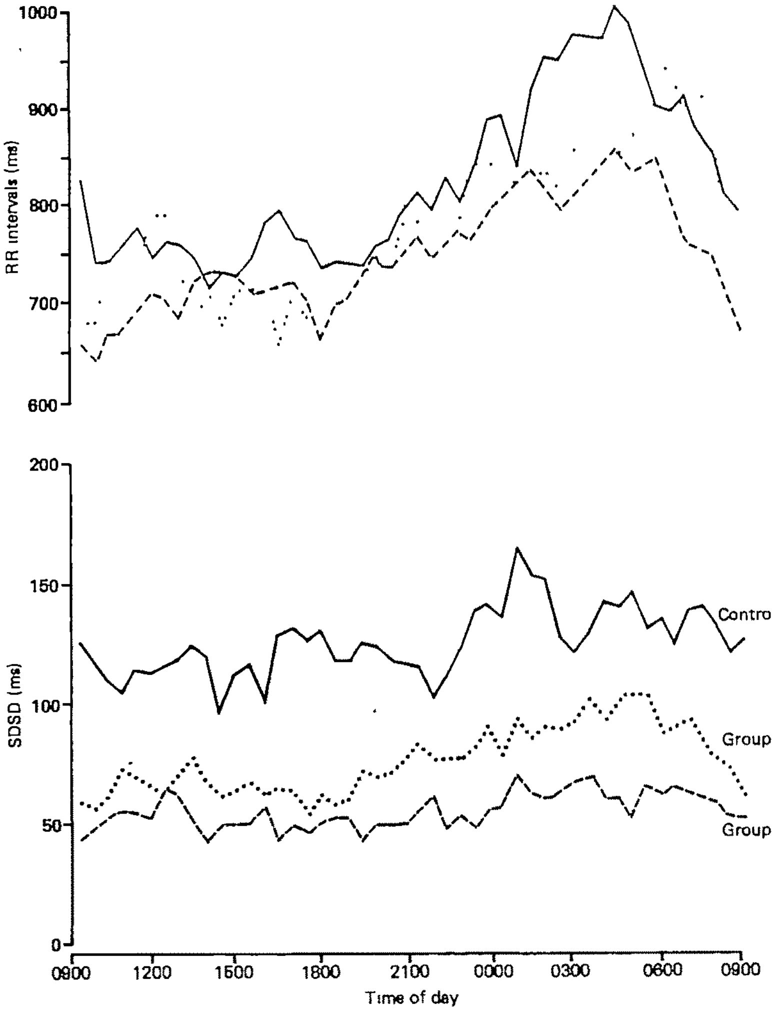

Figure 2 Individual mean heart rate variability (SDSD) in the three groups for the whole 24 h period. The solid line indicates the mean value in each group. There was a significant difference between controls and both alcohol dependent groups that the standard tests of autonomic function did not identify.

Table 2 Mean heart rate variability (SDSD) over six time periods in 11 controls, 16 alcohol dependent men without vagal neuropathy (group 1), and seven alcohol dependent men with vagal neuropathy (group 2) (mean (SEM))

	Controls	*Group 1*	*Group 2*
Morning (0900–1130 h)	125 (12)	72 (11)	58 (10)
Lunch (1130–1400 h)	117 (16)	70 (10)	53 (9)
Afternoon (1400–1730 h)	126 (13)	68 (9)	50 (10)
Evening (1700–0000 h)	134 (16)	81 (11)	58 (11)
Sleep (0000–0530 h)	152 (17)	100 (17)	71 (20)
Waking (0530–0900 h)	140 (20)	94 (17)	69 (18)

mean RR interval over 24 h was 806 (38) ms in the controls, 773 (29) ms in group 1, and 739 (23) ms in group 2.

Heart rate variability was significantly lower ($p < 0{\cdot}01$) in both alcohol dependent groups than in the controls at all times over the 24 h period; however, the alcohol dependent groups were not significantly different from each other. The heart rate variability did not show the same degree of periodicity over 24 h as the RR intervals and no clear variation was apparent (fig 1). When the mean of the heart rate variability for morning, lunch, afternoon, evening, sleep, and waking was taken a tendency for variability to increase during sleep was seen (table 2). The increase during sleep was similar in all groups and only set at a lower point in alcohol dependent groups. The mean SDSD over 24 h was 138 (10) ms in the normal group, 83 (11) ms in group 1, and 60 (12) ms in group 2 (fig 2). Twenty four hour SDSD values for 12 out of 16 of the group 1 men were well below the mean SDSD of the controls. Sixteen of the 23 alcohol dependent men had Valsalva ratios within the normal range, 10 had normal responses on standing, 12 for deep breathing, and nine in response to neck suction. Only six of the 23 alcohol dependent men had mean heart rate variability values within the normal range; this was significantly less than the proportion with normal tests of autonomic function.

Discussion

Heart rate variability was significantly reduced in alcohol dependent men with established vagal neuropathy and in some without. One explanation is that measurement of 24 h heart rate variability detected subtle changes in autonomic integrity in the men in whom standard tests of autonomic function were normal. The difference in the proportion of alcohol dependent men with heart rate variability or autonomic function test results within the normal range accords with this explanation and indicates that grouping alcohol dependent people according to the presence of autonomic neuropathy may hide important information. Our results were consistent with earlier evidence in diabetic patients[8] that 24 hour monitoring of heart rate variability detected small changes in autonomic function which may not be detectable by standard autonomic function tests.

Alternatively the similarity between heart rate variability in the alcohol dependent men with normal autonomic function and with abnormal autonomic function may relate to disordered end organ function. Tests of autonomic function measure the end organ responses to reflex stimulation; therefore conclusions about the origin of abnormal responses are made from indirect measurements. In this study minor subclinical cardiomyopathy may have been present in a few men; this was not excluded by a chest *x* ray or echocardiogram. Though Levin noted decreases in the Valsalva ratio in individuals with clinically overt cardiomyopathy[12] the effect of subclinical cardiomyopathy on autonomic function has not been documented. The SDSD index of heart rate variability may be more affected by subclinical cardiomyopathy and the reduced heart rate variability in some alcohol dependent men with normal standard autonomic function tests may be the result of subclinical cardiomyopathy rather than vagal neuropathy. Previous studies of alcoholic vagal neuropathy did not exclude individuals with cardiomyopathy,[1 2 13] which is quite common in this group.[14] It is unlikely, however, that cardiomyopathy accounts for all the reduction in heart rate variability in the alcohol dependent men with normal autonomic function tests, and some degree of vagal neuropathy is feasible. Because of these possibilities it may be inappropriate to apply autonomic function tests to alcohol dependent individuals. In future studies alcohol dependent individuals should be excluded if results are to be considered a reflection of vagal function.

In alcohol dependent individuals the risk of death was increased in those with vagal neuropathy.[15] Most deaths in the study were sudden or unexplained. A reduced heart rate variability over 24 hours was associated with a 5·3 fold increase in the mortality in patients recovering after myocardial infarction.[16] Furthermore heart rate variability was reduced in patients known to be at risk of sudden cardiac death.[17] The rise in heart rate variability during sleep that we found has been noted before.[8] This may confer some extra stability on the sinoatrial axis because the arrhythmias decreased during orthodox slow wave sleep.[18] It has been suggested that the integrity of the autonomic nervous system may be important in the prevention, promotion, or precipitation of cardiac arrhythmias and that reduced vagal efferent activity may favour cardiac electrical instability.[19] Measurement of heart rate variability over 24 hours may be an appropriate means of assessing such alterations.

Twenty four hour measurement of heart rate variability is potentially an accurate test of autonomic function. This is gained by the addition of every RR interval occurring in 24 hours (up to 140 000 beats per day) and through the measurement of heart rate variability by the SDSD which is unaffected by periods of activity. The SDSD has been used as a method for assessing short term heart rate variability in newborn infants[20] and in individuals with multiple sclerosis and diabetes[21 22] but its application to 24 hour electrocardiographic recordings has been limited.[8] Its sensitivity and statistical robustness when applied to ventricular extrasystoles has been critically examined.[23] The SDSD acts as a statistical filter in which the low frequency components such as trends in heart rate caused by activity and neurohormonal effects are filtered out. Its interpretation therefore relies on the reproducibility of a stimulus, the cooperation of subjects, and the long term stability of the timing mechanisms in the recording equipment. Thus though the alcohol dependent groups had higher heart rates this would not account for the reduced heart rate variability. Neubauer and Gundersen proposed that the SDSD was the best method of detecting small and early abnormalities in autonomic function.[21] The SDSD produces a measure of beat to beat variability and is a composite of variability of all the higher frequencies present in the data that could be identified by other methods such as spectral analysis.[24] This composite emphasises the higher frequencies because lower frequency variation due to blood pressure and thermoregulatory mechanisms usually causes minimal beat to beat changes that are not autonomic in origin. For these reasons the SDSD is likely to be a more accurate measure of autonomic function than the standard deviation of the RR intervals.[16] It is also more appropriate for examining ambulatory autonomic function than spectral analysis because several constraints make spectral techniques unsuitable in examining all forms of data on the RR interval.[25] The period of sleep is the most basal state of the day. Ambulatory monitoring provides an opportunity to examine cardiac autonomic function during this time. It is likely to be a reflection of natural background stimuli rather than the artificial manoeuvres conducted in laboratory based tests.

Tests of autonomic function have generally been developed and validated by application to patients with diabetes mellitus. There have been few examinations of heart rate variability in alcohol dependent patients[13] and no previous long term recordings. Commonly used autonomic tests cause a temporary imbalance of the system examined, do not reflect its steady state function, and require active participation from the patient. These tests do not generally allow for the accurate detection of quantitative abnormalities in autonomic function beyond the description of abnormal or normal, though some attempts have been made to do so.[5] Alcoholic polyneuropathy is generally accepted to be a result of nutritional factors rather than a neurotoxic effect of alcohol.[26] The reported improvement in autonomic function with prolonged abstinence may be due to improved nutrition in some alcohol dependent patients.[5] Provided cardiomyopathy is excluded, 24 hour monitoring may overcome many of the problems with conventional tests for measuring changes in cardiac autonomic function in alcohol dependent patients.

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Pulmonary microvascular permeability in patients with severe mitral stenosis

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Abstract

Patients with rheumatic mitral stenosis often have no pulmonary oedema despite considerably increased pulmonary venous pressure. Pulmonary microvascular permeability was measured non-invasively by a previously validated method of double isotope scintigraphy with indium-113m and technetium-99m. This permits calculation of an index reflecting transferrin efflux and thus, indirectly, the microvascular permeability. Fifteen patients with severe mitral stenosis (defined as valve area $<1{\cdot}0$ cm^2) were compared with a control group of 11 patients with mild coronary artery disease. The permeability index was significantly lower in patients with mitral stenosis than in the control group. Furthermore, the extent of reduction of the permeability index correlated with the severity of mitral stenosis as reflected by the Gorlin valve area.

This finding may account for the relative resistance of these patients to pulmonary oedema despite chronic pulmonary venous hypertension.

Patients with mitral stenosis have a surprising resistance to pulmonary oedema despite persistently increased pulmonary venous pressure, and pulmonary oedema may only appear terminally or as a complication of fast atrial fibrillation.[1] In patients with myocardial infarction, a rapid increase in pulmonary venous pressure to ≥ 20 mm Hg (measured from mid-chest level) results in the formation of pulmonary oedema.[2 3] In patients with mitral valve disease, however, pulmonary venous pressure can rise gradually to $\geqslant 30$ mm Hg without the development of overt pulmonary oedema[4 5]—though women with mild or moderate mitral stenosis (valve area $>1{\cdot}5$ cm^2) in whom acute pulmonary oedema develops during pregnancy are a possible exception.

Two main hypotheses have been advanced to explain this resistance to pulmonary oedema in patients with mitral stenosis. First, a decrease in pulmonary microvascular permeability might be the protective mechanism. Alternatively pulmonary oedema might be prevented by increased lymphatic flow, capillary permeability being normal or even increased as a result of vascular damage. To investigate these hypotheses we estimated pulmonary microvascular permeability by the non-invasive technique of double isotope scintigraphy, first described by Gorin *et al*[6] and subsequently modified by Basran *et al*.[7] In invasive experiments in sheep, the plasma protein accumulation index thus obtained closely paralleled the concentration of protein measured in the lymph draining from the lung.[6] The plasma protein accumulation index therefore provides a non-invasive measure of pulmonary microvascular permeability and we used it in the present study to examine the hypothesis that resistance to pulmonary oedema in mitral stenosis is the result of decreased pulmonary microvascular permeability.

Patients and methods

PATIENTS

The study was approved by the local ethics committee and all subjects gave their written consent. We studied 15 patients undergoing cardiac catheterisation for the assessment of longstanding mitral stenosis. Each had had moderate to severe exertional dyspnoea (Canadian Cardiovascular Society grade 2 or 3) for 4–14 years. Patients had either pure mitral stenosis or dominant mitral stenosis with mild mitral regurgitation, and in all of them the valve area calculated by the Gorlin formula was $<1{\cdot}0$ cm^2. The diagnosis of rheumatic stenosis was based on a history of past rheumatic fever and the typical M mode echocardiographic features of leaflet thickening and commissural fusion. There was no other valve disease or cardiac abnormality and no evidence of primary lung disease.

We measured the plasma protein accumulation in 11 patients who had mild or moderate coronary artery disease with normal left ventricular function, as judged by ventriculography and normal left ventricular end diastolic pressure (<10 mm Hg). M mode and cross sectional echocardiography were normal in all of them. Six of these were smokers (5–10 cigarettes per day) but all had normal lung function tests and no evidence of primary lung disease.

PROTOCOL

Before cardiac catheterisation each patient underwent full clinical assessment, electrocardiogram, chest *x* ray, and echocardiography. Lung function testing included spirometry, single-breath carbon monoxide diffusing capacity measurements (DL_{CO} and K_{CO}), and plethysmographic lung volume measurements. In 10 of the patients with

Table 1 Baseline cardiopulmonary data (median (range)) in controls and patients with mitral stenosis

	Mitral stenosis		*Controls*	
Age (yr)	61	(37–77)	56	(36–65)
Sex	4 M, 11 F		5 M, 6 F	
FEV_1 (l)	2·1	(1 5–2 6)	2 9	(2 3–3 3)
FVC (l)	2 6	(2 1–3·0)	3 7	(3 3–4 5)
DM (% of predicted)	26	(17–39)	107	(79–127)
VC (% of predicted)	120	(65–172)	108	(86–128)
Mitral valve area (cm^2)	0 65	(0 39–0 98)	—	
Mean PA pressure (mm Hg)	43	(32–80)	20	(17–26)
Mean PW pressure (mm Hg)	27	(21–40)	7	(5–10)
LVEDP (mm Hg)	7	(4–10)	5	(2–8)
LVEF (%)	65	(60–71)	66	(60–71)

DM, diffusing conductance, FEV_1, forced expiratory volume in one second; FVC, forced vital capacity, LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; VC, capillary blood volume; PA, pulmonary artery, PW, pulmonary capillary wedge.

mitral stenosis and in eight of the controls the diffusing conductance (DM) of the alveolar-capillary membrane and the accessible pulmonary capillary blood volume (VC) were determined by the method of Roughton and Forster,[8] and K_{CO} was measured at oxygen saturations of 21% and 100%.

SCINTIGRAPHY

Pulmonary microvascular permeability was assessed by measuring the plasma protein accumulation index, which is based on the pulmonary accumulation of radiolabelled transferrin (molecular weight 88 000). This was measured by external radiation detectors, and by correcting for any changes in circulating blood volume by simultaneously monitoring radiolabelled autologous red blood cells. A modification of the protocols of Gorin[6] and Basran[7] was used to label transferrin in vivo by intravenous injecton of 100 MBq of indium–113m chloride solution from a sterile generator. Red blood cells were labelled in vivo by the intravenous injection of 0 02 mg per kg body weight of stannous fluoride with 0·024 mg per kg body weight of sodium medronate, and then after a delay of 15 minutes, 100 MBq of technetium–99m pertechnetate from a sterile generator. After these intravenous injections, count rates from both radionuclides were monitored in the supine patient by a large single-crystal gamma camera placed posteriorly under the thorax and a portable probe over the anterior chest wall. The probe acquired data from an area approximately 8 cm in diameter and was placed alternately over the cardiac area and the right upper zone. The duration of scanning necessary for significant results was 90 minutes.

ANALYSIS

The ratio of indium–113m activity to technetium–99m activity was calculated for each area, after correction for down-scatter from indium 393 keV to the technetium window 141 keV. This ratio counted over the lung fields was then divided by the same ratio counted over the cardiac area, and the overall quotient was plotted against time. The plasma protein accumulation index is defined as the slope of this relation and reflects transferrin efflux and accumulation in the lung fields.[6 7] The slope of the best-fit straight line was determined by computed linear regression analysis according to the method of least squares.

A regional image of plasma protein accumulation index was obtained from the gamma camera data; each pixel corresponded to a square of side 12 mm on the thorax of the patient. By defining regions of interest corresponding to each lung, all enclosed pixels were averaged to obtain a mean plasma protein accumulation index for the individual patient.

Distribution-free statistics have been used throughout. Values are given as median ± semi-interquartile range, patient groups were compared but the Mann-Whitney U statistic, and correlations were examined by the Spearman rank correlation coefficient R.

Results

GROUP CHARACTERISTICS

We studied 15 patients with mitral stenosis (four men and 11 women, aged 37–77 (median 62)). The five men and six women in the control group were aged 36–65 (median 56). The patients with mitral stenosis were thus slightly older than the controls, and, as expected, were predominantly female. All were in established atrial fibrillation, unlike the controls all of whom were in sinus rhythm.

LUNG FUNCTION

As expected the patients with severe mitral stenosis had reduced lung volumes (table 1). The results for diffusing conductance of the alveolar-capillary membrane and for the accessible pulmonary capillary blood volume showed a wide range of values and in this small group of patients were not related to age, sex, or severity of mitral stenosis.

HAEMODYNAMIC VARIABLES

Left ventricular function as reflected by ejection fraction and end diastolic pressure was similar in the two groups (table 1). The patients with mitral stenosis all had a considerable increase in mean pulmonary artery wedge pressure to between 21 and 40 mm Hg. The mean mitral valve gradient for 10 cycles was between 8 and 18 mm Hg, reflecting critical reductions in calculated

Table 2 Plasma protein accumulation (PPA) index results

		PPA index ($\times 10^{-3}$) per minute			
Group	*No*	*Maximum*	*Minimum*	*Median (± semi-interquartile range)*	
Severe mitral stenosis	15	+0 30	−1 70	0·0 ± 0 27	p < 0 02
Controls	11	+1 00	−0 25	+0 3 ± 0 32	

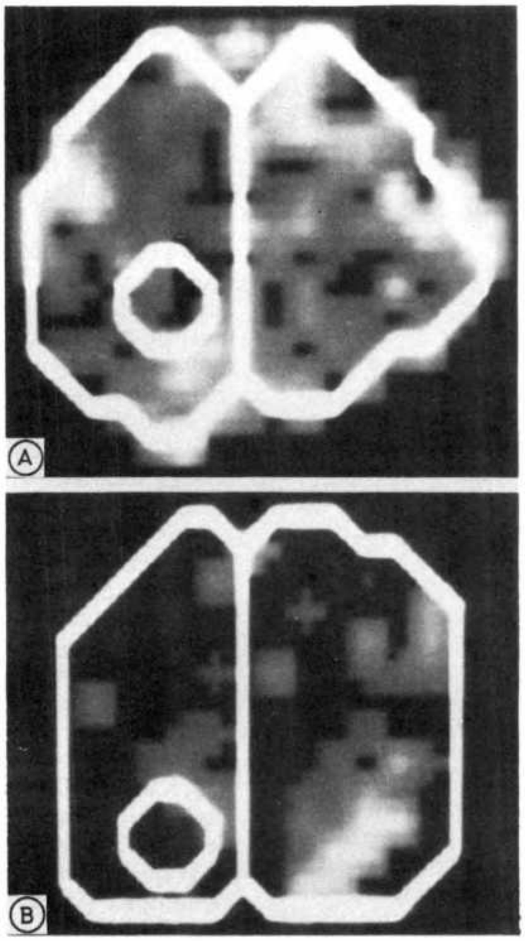

Figure 1 Examples of regional plasma protein accumulation images in (A) a control subject and (B) a patient with severe mitral stenosis.

valve area (formula of Gorlin and Gorlin) which was < 1·0 cm^2 in every patient. In most there was also mitral regurgitation—mild (grade 1) in nine patients but moderate (grade 2 or 3) in four. Eleven of the patients subsequently underwent mitral valve replacement.

PULMONARY MICROVASCULAR PERMEABILITY

Figure 1 shows examples of the regional images of plasma protein accumulation index throughout both lung fields. In the controls (without mitral valve disease or left ventricular impairment) there was considerable variation from pixel to pixel, but no consistent regional pattern, and this is attributed to the low absolute number of counts from each small pixel area resulting in noise. In the patients with mitral stenosis there was again some heterogeneity in the image but no regional pattern; the average pixel values were lower than in the controls, as is apparent from fig 1. This difference between the groups is confirmed by calculation of the mean plasma protein accumulation index of the lung fields in each individual patient (fig 2). Though there was a wide range of individual plasma protein accumulation values in each group and considerable overlap between the groups, the difference between the group medians was significant ($p < 0·02$). Moreover, within the mitral stenosis group the mean plasma protein accumulation index and the severity of mitral stenosis as reflected by the Gorlin mitral valve area were strongly correlated ($R = +0·7$, $p < 0·01$) (fig 3).

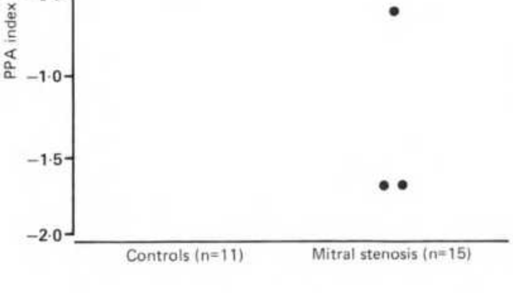

Figure 2 Mean plasma protein accumulation index for individual patients.

There were no significant correlations between the plasma protein accumulation index and any other haemodynamic or lung function variables. In particular there was a trend towards correlation with the mean pulmonary wedge pressure (fig 4) that did not attain statistical significance.

Discussion

The patients with mitral stenosis included in this study all had severely reduced valve areas, but despite significant increases in pulmonary artery wedge pressures and dilatation of the upper lobe veins none had radiographic evidence of interstitial pulmonary oedema. In this study we used a previously validated double isotope scintigraphic method to evaluate pulmonary microvascular permeability non-invasively in these patients. Regional images and mean values of an index of ^{113m}In-labelled transferrin accumulation in the lung over a 90 minute period gave an indirect measure of plasma transferrin efflux—the plasma protein accumulation index—reflecting the microvascular permeability. The data showed that in severe mitral stenosis the plasma protein accumulation index was significantly less than in controls with normal mitral valves and normal left ventricular function. Furthermore, the degree to which the plasma protein accumulation index was reduced correlated closely with the severity of mitral stenosis as judged by the calculated valve area. The patient and control groups were of comparable age, but there were more women in the patient group.

We found a wide range of values of the mean plasma protein accumulation index for the individuals within each group and considerable overlap between the groups (fig 2). In some subjects the detected counts showed considerable fluctuation during the acquisition period, and when linear regression was used to find the best-fit straight line, the result was a negative plasma protein accumulation index. We attribute this to the high noise-to-signal ratio of this dual isotope method; our range of values in

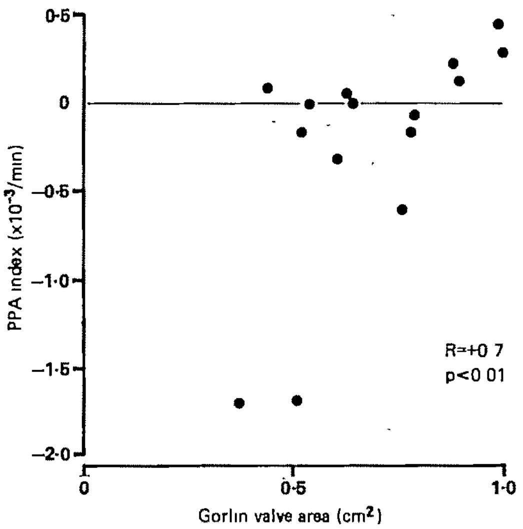

Figure 3 Relation between plasma protein accumulation index and the severity of mitral stenosis.

the control group was similar to those reported by other workers.[7 9]

Factors affecting the formation of pulmonary interstitial fluid are described by the Starling equation,[10] which may be written:

$$F/A = K(\Delta P - s.\Delta\Pi)$$

where F/A is the net rate of flow from capillary lumen to interstitial space per unit area of capillary wall, ΔP is the difference in hydrostatic pressure, ΔΠ is the difference in colloid osmotic pressure, K is the apparent liquid filtration coefficient (hydraulic conductivity), and s is the reflection coefficient for colloids at the capillary wall. The pulmonary capillary hydrostatic and osmotic pressures are relatively easily estimated (as pulmonary wedge pressure and plasma colloid osmotic pressure) and their independent influences on the development of pulmonary oedema are now well established.[11 12] The other terms are difficult to measure non-invasively in humans but may be equally important in determining pulmonary oedema. Changes in pulmonary microvascular permeability have been postulated in cases of pulmonary oedema related to hypoxia,[13] adult respiratory distress syndrome,[14] pulmonary embolism,[15] and lung re-expansion.[16] Indirect evidence of capillary permeability changes in pulmonary and renal beds has recently been reported in patients with adult respiratory distress syndrome.[17] Increased pulmonary microvascular permeability was measured more directly in animal studies when pulmonary oedema was induced by haemorrhagic shock or by inhaled or circulating toxins.[18–20]

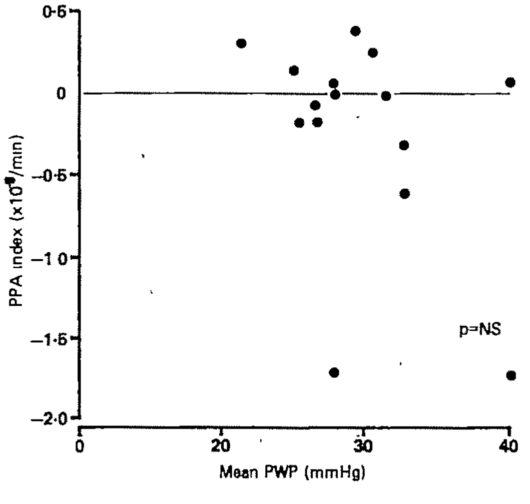

Figure 4 Lack of relation between plasma protein accumulation index and the mean pulmonary capillary wedge pressure

Because our patients had normal plasma oncotic pressures (as reflected by albumin and total protein concentrations) the mechanism protecting against pulmonary oedema in the face of high capillary hydrostatic pressures must lie in complex alterations in pulmonary interstitial pressures favouring fluid retention within the vascular space, reduced pulmonary microvascular permeability (embraced by the K and s parameters in the Starling equation above), or increased and rapid lymphatic drainage of interstitial fluid.

Interstitial pressures in the lung cannot be measured clinically and their role, if any, in protecting against oedema formation in mitral stenosis remains unknown. Direct measurement of pulmonary microvascular permeability has also been impossible but it has long been suspected that reductions in permeability might be the protective mechanism. Since 1936, numerous investigators have reported appreciable thickening of the layer between the capillary lumen and the alveolar gas space in patients with mitral stenosis,[21–23] but there have been no studies to evaluate the physiological significance of this histological observation. The double isotope scintigraphic technique developed by Gorin[6] and modified for use in patients by Basran[7] is a non-invasive method that is ideally suited to this purpose. Our finding that the plasma protein accumulation index in patients with mitral stenosis was significantly less than in controls suggests that the rate of transferrin efflux was reduced by parallel reductions in pulmonary microvascular permeability.

The changes in the pulmonary microcirculation in mitral stenosis have attracted much attention, and the explanation of the resistance to pulmonary oedema has been the subject of debate.[24–26] Though the Starling equation describes the principal determinants of fluid flux across the capillary wall, the level of interstitial fluid also depends on the dynamics of lymphatic flow draining protein and fluid back into the circulation. Thus increased lymphatic flow might protect against pulmonary oedema. Indeed, there was histological evidence of dilated pulmonary lymphatic vessels in biopsy material from patients with chronically raised left atrial pressure.[27 28] Moreover, in animal models of chronic pulmonary venous hypertension, considerable increases in pulmonary lymphatic flow were reported[29] though the correlation with lung water was generally poor.[30]

Does our finding of a reduced plasma protein accumulation index in severe mitral stenosis reflect rapid clearance of the radiotracer in a hyperdynamic lymphatic system, rather than altered pulmonary microvascular permeability? This interpretation of our data is not supported by the original animal experiments in which double isotope scintigraphy was used to examine protein fluxes in the lung.[6] In these experiments it was found that the plasma protein accumulation index closely paralleled the protein concentrations in pulmonary lymph (and thus pulmonary microvascular permeability) rather than the volume of lymphatic flow. Based on these data, the reduction in plasma protein accumulation index in our patients with severe mitral stenosis indicates reduced pulmonary microvascular permeability rather than increased lymphatic clearance.

CONCLUSIONS

Pulmonary microvascular permeability, as measured by the plasma protein accumulation index of transferrin efflux, was significantly reduced in severe mitral stenosis. Furthermore, the extent of this reduction correlated with the severity of the mitral stenosis, as reflected by the calculated valve area. The resistance to pulmonary oedema of patients with severe rheumatic mitral stenosis may at least in part be attributable to a decrease in pulmonary microvascular permeability. It is, however, likely that other mechanisms also contribute, such as increased left atrial size and compliance and increased pulmonary lymphatic drainage.

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Syndrome X and hyperventilation

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Abstract

The cardiorespiratory responses to exercise and forced hyperventilation were measured in 17 unselected patients with syndrome X (angina, positive exercise test, normal coronary arteriogram, no other cardiovascular disease) and compared with those in 15 healthy subjects. Forced hyperventilation produced hypocapnia and metabolic alkalosis but no chest pain or electrocardiographic change. Patients with syndrome X showed reduced maximum oxygen consumption with an increased respiratory exchange ratio at peak exercise, confirming that exercise was limited by skeletal muscle perfusion—and thus that the increase in cardiac output with exercise is limited in syndrome X as in heart failure. Arterial carbon dioxide tension (P_{CO_2}) homoeostasis during exercise was normal but the ventilatory cost of carbon dioxide excretion was increased in syndrome X (as in heart failure). End tidal P_{CO_2} measurements correlated only poorly with arterial P_{CO_2} in individual patients with syndrome X, providing a possible explanation for previous reports, based on end tidal P_{CO_2}, of inappropriate hyperventilation.

Patients with syndrome X did not show inappropriate hyperventilation but they did show hyperventilation that was appropriate to maintain normal arterial P_{CO_2} in the face of reduced cardiac reserve.

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Most patients with chest pain and normal coronary arteriography have non-cardiac pain that is musculoskeletal or oesophageal in origin.[1 2] A few are thought to have true angina attributable by inference to an impaired coronary dilator response at the microvascular level (syndrome X)[3 4] though in the absence of a directly documented vascular abnormality or known pathogenetic mechanism the existence of this syndrome is not universally accepted. Because of this uncertainty, some have ascribed the symptoms to hyperventilation,[5–7] which would accord with the low end tidal partial pressure of expired carbon dioxide.[7] Hyperventilation has indeed been shown to induce electrocardiographic ST segment depression,[8] and alkalosis that is associated with hyperventilation can induce coronary vasoconstriction.[9] To investigate the possible contribution of hyperventilation in these patients, we studied the cardiorespiratory response to exercise and hyperventilation in an unselected group of patients with syndrome X (defined as typical stable effort angina, a positive exercise test, and a normal coronary arteriogram in the absence of other cardiovascular disease).

Patients and methods

PATIENTS

We studied 17 patients (mean age 50 years, range 40–67 years; eight men), all of whom gave an independently confirmed history considered to be typical of effort angina (mean duration 3·9 years) with no other evidence of cardiovascular disease on clinical examination, chest radiograph, echocardiogram, or left ventricular angiogram; and in all of whom the coronary arteriograms were independently confirmed as entirely normal. No patient had hypertension or diabetes. Two patients smoked, and five were ex-smokers. Eleven patients were taking regular medication (four with β blockers, seven with calcium antagonists, four with long acting nitrates). The resting electrocardiogram was normal except in three patients with left bundle branch block. Exercise tolerance was limited in all patients, to the equivalent of New York Heart Association category II (15 patients) or III (two patients): in all patients treadmill exercise showed diagnostic ST segment depression ($\geqslant$ 1 mm horizontal or downsloping ST segment) or left bundle branch block (in five patients, exercise-related in two). All patients had normal respiratory function tests (spirometry, lung volumes, and transfer factor).

We studied 15 healthy individuals (mean age 47 years, range 22–75 years, eight men) as controls.

PROTOCOL

Patients and controls performed maximum treadmill exercise tests (Weber or standard Bruce protocol, selected as appropriate for exercise capacity) and 3 minutes of forced hyperventilation after familiarisation with the procedures (with 30 minute rest periods preceding each procedure) >2 hours after a meal and >24 hours after stopping medication. The study was approved by the local ethics committee.

Respiratory gas exchange was measured as decribed elsewhere.[10] During the first exercise test, expired gas from a face mask (Hans Rudolph 7900) was carried to a 7 litre mixing

Table Heart rate, systolic blood pressure, maximum oxygen consumption, respiratory exchange ratio ($n = 17$) and arterial and end tidal gas measurements ($n = 13$) from both exercise tests in patients with syndrome X. (The mean data for patients without left bundle branch block are given in italic and in parentheses, $n = 12$ and 9 respectively.)

	Rest	*50% of maximum exercise*	*Maximum exercise*
Heart rate (per min)	81 (16) *(74)*	—	135 (26) *(128)*
SBP (mm Hg)	125 (13) *(126)*	—	160 (22) *(160)*
V_{O_2} max (ml/min/kg)	—	—	20·1 (4·4) *(20·1)*
RER	0·7 (0·1) *(0·7)*	—	1·1 (0·1) *(1·1)*
CO_2 ET (mm Hg)	35 (4) *(35)*	38 (4) *(38)*	37 (4) *(37)**
Pa_{CO_2} (mm Hg)	37 (4) *(37)*	39 (4) *(39)*	36 (3) *(36)**
pH	7·43 (0·04) *(7·44)*	7·42 (0·03) *(7·41)*	7·40 (0·06) *(7·39)*
Bicarbonate (mmol/l)	26 (1) *(26)*	25 (1) *(25)*	24 (3)* *(23)*
Pa_{O_2} (mm Hg)	92 (13) *(93)*	92 (7) *(91)*	100 (9)* *(100)*

SBP, systolic blood pressure; V_{O_2} max, maximum oxygen consumption, RER, respiratory exchange ratio (V_{CO_2}/V_{O_2}), CO_2ET, end tidal P_{CO_2}, Pa_{CO_2}, arterial P_{CO_2}, Pa_{O_2}, arterial P_{O_2}.
*$p < 0·05$ compared with resting value (analysis of variance)

box (Airspec) to allow measurement of minute ventilation, oxygen consumption, and carbon dioxide elimination by argon dilution and mass spectrometry (Airspec 2200) corrected to standard temperatures and pressures dry.[11] During the second exercise test and the forced hyperventilation test a capillary tube continuously sampled expired air from within the face mask to measure respiratory rate and end tidal oxygen and carbon dioxide, averaged over the sampling period of 30 seconds; end tidal carbon dioxide values were corrected as previously described.[12] Heparinised arterial blood samples were taken during all these procedures (via an indwelling arterial cannula inserted 30 minutes before any measurement) for blood gas analysis in 13 of the 17 patients.

The relation of minute ventilation to minute carbon dioxide production during exercise was analysed by linear regression. Data are presented as mean (1 SD). Repeated measures in the same individual were analysed by analysis of variance. Other data were compared by paired or unpaired Student's *t* test as appropriate. Probability values of $< 0·05$ were regarded as significant.

Results

During voluntary forced hyperventilation the respiratory rate increased (from 12(5) to 31(7) per minute), arterial P_{CO_2} and end tidal P_{CO_2} fell (from 36(4) to 23(5) mm Hg and from 33(3) to 20(6) mm Hg, respectively), and pH increased (from 7·4(0·04) to 7·6(0·10)), without chest pain or electrocardiographic change in any individual.

The table shows the exercise test data for patients with syndrome X. The patients had similarly limited exercise duration in both tests (10·2(2·6) and 9·9(2·5) minutes), and maximal oxygen consumption was less than in the controls (20·1(4·4) *v* 29·7(7·2) ml/min/kg, $p < 0·001$). Exercise was limited by chest pain in 14 (including two of the patients with fixed left bundle branch block and one with left bundle branch block induced by exercise), and by dyspnoea (a patient with fixed left bundle branch block), fatigue, and hypotension (40 mm Hg fall in systolic blood pressure in a patient with left bundle branch block induced by exercise) in one patient each. In all these patients there was diagnostic electrocardiographic evidence of myocardial ischaemia or left bundle branch block. At maximum exercise the respiratory exchange ratio (minute carbon dioxide/minute oxygen consumption) was increased to 1·1 (0·1) as in the healthy controls (compared with 0·7 (0·1) at rest). At peak exercise, there were very small reductions in arterial P_{CO_2}, bicarbonate, and pH, reflecting a compensated metabolic acidosis; but arterial P_{CO_2} was normal at 50% maximum exercise. There was thus no evidence of inappropriate hyperventilation.

The relation between minute ventilation and minute carbon dioxide (VE/V_{CO_2}) on exercise was linear in all syndrome X patients (all $r \geqslant 0·92$) as it was in the healthy controls (figure); the slope (m) of this relation was, however, significantly steeper (32·3(4·6) *v* 26·2(5·0), $p < 0·01$), though the minute ventilation axis intercepts (c) were similar (2·6(1·9)l/min *v* 2·6(2·2)l/min). The ventilation required for carbon dioxide elimination was thus increased in patients—for example at a minute carbon dioxide production of 1 l/min, it was 34·9(4·2) compared with 27·9(4·3) l/min in the healthy controls ($p < 0·001$). In individual syndrome X patients end tidal P_{CO_2} correlated poorly with arterial P_{CO_2} both at

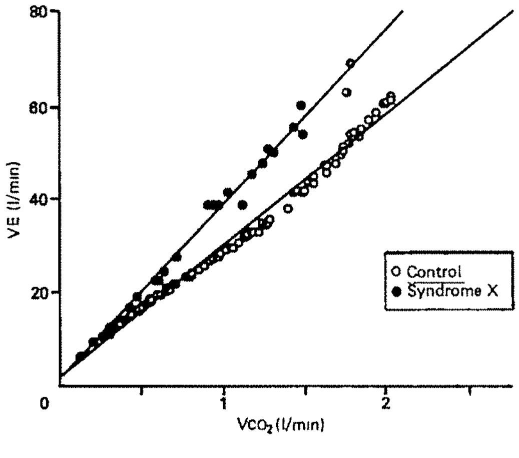

Figure Relation between minute ventilation and minute carbon dioxide production during exercise in a healthy control and a patient with syndrome X. Minute ventilation axis intercepts were similar in both, but the slope (37·5) was steeper in syndrome X than in the healthy control (28·2). The r values of both linear regressions are 0·99. VE, minute ventilation; V_{CO_2}, minute carbon dioxide production.

rest (r = 0·36, NS) and during exercise (r = 0·44, NS), though it correlated well during forced hyperventilation (r = 0·86, $p < 0·001$).

The findings did not differ in patients with left bundle branch block and without. For the 12 patients without left bundle branch block (mean age 49 years, range 40–67 years, five men) the exercise duration in the two tests were 10·1(1·4) and 9·9(1 8) minutes and exercise was limited by chest pain in 11 and fatigue in one. Haemodynamic changes, maximum oxygen consumption, and arterial gas changes during exercise were similar in the 12 patients without left bundle branch block (see table), as were the minute ventilation/minute carbon dioxide relations (slope, m = 33·2(4·5), $p < 0·01$ compared with controls; ventilation axis intercept, c = 2·7(1·9)l/min).

Discussion

Since the advent of coronary angiography, reports on patients with "chest pain with normal coronary arteries" have accumulated, but the patients have not always been rigorously characterised nor have there been agreed criteria to define such patient groups. Among possible causal mechanisms for the symptoms, hyperventilation has been suggested with supportive evidence from measurements of end tidal Pco$_2$.

We therefore investigated a group of patients selected solely because they fulfilled predefined criteria for what has come to be known as syndrome X. We included patients with exercise induced or fixed left bundle branch block because in patients with syndrome X left bundle branch block can develop; analysis of the data showed similar findings whether or not patients with left bundle branch block were included.

Voluntary forced hyperventilation caused the expected reduction in arterial Pco$_2$ and respiratory alkalosis but it did not induce chest pain or electrocardiographic change. The patients were therefore studied during formal exercise testing. As in the healthy controls, arterial Pco$_2$ was maintained within a narrow range by matching the ventilatory clearance of carbon dioxide to its increased metabolic rate of production.[13 14] At maximum exercise there was only a small reduction in arterial Pco$_2$, compensating for the onset of anaerobic metabolism.[13 14] There was no evidence of altered arterial Pco$_2$ setpoint or inappropriate hyperventilation either at rest or during exercise. Inappropriate hyperventilation thus does not seem to be the cause of symptoms in patients with syndrome X as here defined.

Patients with syndrome X, however, showed reduced maximum oxygen consumption, with metabolic acidosis at peak exercise, implying that exercise was limited by perfusion to the exercising skeletal muscle as in heart failure; this is consistent with reported evidence of cardiac dysfunction in syndrome X.[15 16] Moreover, the ventilatory cost of carbon dioxide clearance was increased in patients with syndrome X, a finding also characteristic of patients with congestive heart failure.[17 18] The increase in carbon dioxide production resulting from the increased work of exercise, the increased respiratory exchange ratio as anaerobic metabolism developed at peak exercise, and the increased ventilation needed to excrete carbon dioxide all contributed to increased ventilation in these patients—or what might be called appropriate hyperventilation because it maintained normal arterial Pco$_2$.

End tidal Pco$_2$ values correlated well with arterial Pco$_2$ values in the group as a whole, as was reported in healthy controls, but the correlation in individuals was poor (except during forced hyperventilation). This is consistent with the increase in physiological deadspace implied by the increased ventilatory cost of carbon dioxide excretion in these patients.[13] Practically, it indicates that measurements of end tidal Pco$_2$ cannot be used as an indicator of arterial Pco$_2$ in individual patients with syndrome X, as was done in earlier studies that suggested that hyperventilation was a common cause of symptoms in patients with "chest pain" and normal coronary arteries.[7]

We found no evidence of inappropriate hyperventilation in patients with syndrome X, but we did find evidence of appropriate hyperventilation that seemed to result from an increase in physiological deadspace as is typical of other patients with reduced cardiac reserve.

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Doppler ultrasound and the silent ductus arteriosus

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Abstract

A clinically undetectable, small ductus arteriosus was identified by Doppler ultrasonography in 21 individuals. Infants were excluded from the study and no patient had pulmonary hypertension. Persistence of the ductus arteriosus is likely to be more common than shown by less sensitive diagnostic methods. Some patients considered to have infective endocarditis with a normal heart may have a silent ductus arteriosus. Evidence of such an association would justify ligation or antibiotic cover as prophylactic measures.

The classic continuous murmur of ductus arteriosus is usually sufficient in itself to lead to surgical closure being undertaken. However, the murmur may be atypical in infancy or in the presence of pulmonary hypertension or a large shunt.[1-3] The term "silent duct" was coined to describe the preterm infant with respiratory distress syndrome in whom the ductul murmur is not heard.[4] Doppler ultrasonography has led to the recognition of a small ductus arteriosus with normal pulmonary artery pressure which cannot be identified clinically.

We report our experience in identifying such a "silent duct" in 21 patients examined clinically and by ultrasonography over a three year period.

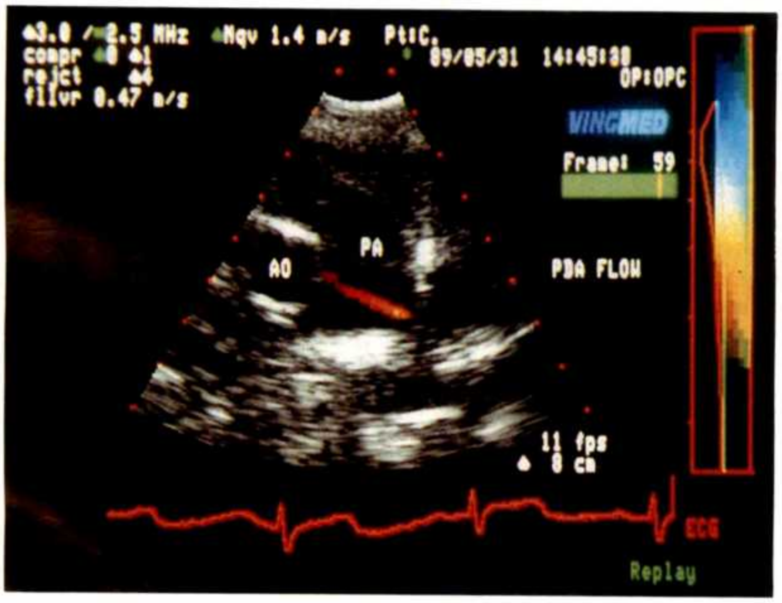

Figure Colour Doppler flow mapping image from a child with a silent ductus arteriosus showing flow from the aorta (Ao) into the pulmonary artery (PA).

Patients and methods

Because of reported difficulties in duct recognition in infants[3] the patients reported on were all more than 12 months old.

We considered that the description of "silent duct" was justified when there was:

(*a*) No continuous or crescendo systolic murmur during normal respiration or deep inspiration. (Patients with a murmur were included if it was typically innocent (including soft midsystolic murmurs in the pulmonary area) or if it was clearly due to another lesion but was so soft that it could not be conducted to the pulmonary area.)

(*b*) No evidence of pulmonary hypertension from clinical, electrocardiographic, and Doppler studies.

(*c*) A characteristic Doppler signal showing continuous flow with a relatively high velocity in diastole recognised by spectral Doppler and recognition of typical ductal flow by colour flow Doppler (when available).

Ultrasound studies were initially performed with an ATL imaging system and a stand alone Vingmed Alfred Doppler system interfaced to a Doptek spectrum analyser. Later we used a Vingmed CFM 700 imaging and colour flow system.

The routine ultrasound study included echocardiographic imaging of systemic and pulmonary veins, intracardiac anatomy, and great artery anatomy; and spectral Doppler measurement of flow velocities through all four valves and the ascending and descending aorta—with a similar colour Doppler flow mapping study to search for any left to right shunt or other abnormality. The ductal spectral signal was recorded by the stand alone or imaging transducer with the transducer in the suprasternal notch or upper left sternal edge. When we used colour Doppler flow mapping, flow was best recorded from a modified short axis view of the great arteries similar to that used to image a duct[5] (fig 1). In some it was better seen from the suprasternal notch with the image showing the aorta in cross section and both the pulmonary artery branches and their confluence.

When Doppler echocardiography showed a ductus arteriosus not suspected on clinical examination the patient was re-examined by two cardiologists; if a systolic crescendo or continuous murmur which might be considered of ductal origin was then heard the patient was excluded from the group.

During the same period a total of 7345 ultrasound studies were performed. Table 1

Table 1 *Age and sex distribution of 21 patients with a silent ductus arteriosus*

Age group (yr)	*Number of cases*			*% in random sample of 360*
	Males	*Females*	*Total*	
1–5	4	4	8	49
6–10	1	6	7	17
11–15	3	2	5	7
Over 15	—	1	1	4

shows the age distribution from a random sample of 360.

Although most children undergoing echocardiography had a murmur there were some with no clinical cardiovascular abnormality, such as patients with Kawasaki disease, Marfan's syndrome, neurological abnormalities associated with cardiac abnormalities, and those on anthracycline treatment in whom left ventricular function was being monitored. Exact numbers of these patients were not recorded. Some patients with innocent murmurs were studied as part of another study. In a sample of 720 consecutive ultrasound studies no cardiac abnormality was detected in 36%.

Results

On the basis of the above criteria we identified clinically silent ducts in 20 children over the age of 12 months who underwent echocardiography during a three year period and in one adult who had an ultrasound scan for demonstration purposes. Six patients had no murmur, two had soft murmurs of other defects, and the remaining 13 had innocent murmurs (table 2). Two had previously undergone surgical ligation of the ductus arteriosus. The distribution of the children was similar in the three age groups of 1–5 years, 6–10 years, and 11–15 years though more younger children had been studied (table 1). In no patient was the duct visible on cross sectional imaging and in all the left ventricular size and function were normal.

Silent ducts were also found in several patients with other defects and relatively loud murmurs but these were not included because of the stringent criteria used for the definition of the "silent duct".

Table 2 *Types of murmur and other clincal findings in 21 patients with a clinically silent ductus arteriosus*

- No murmur (6)
  - Kawasaki disease (1)
  - Marfan's syndrome (1)
  - Tuberous sclerosis (1)
  - Referred with an innocent murmur (1)
  - Five years after ligation of duct (1)
  - Demonstration scan in a 25 year old (1)
- Innocent murmur (13)
  - Soft basal mid-systolic murmur (7)
  - Still's murmur (6)
- Soft murmur of other defect (2)
  - Small muscular ventricular septal defect with a soft pansystolic murmur at the lower left sternal edge (1)
  - Mitral valve prolapse with a soft pansystolic murmur at the apex 13 years after ligation of duct (1)

Numbers of patients are indicated in parentheses.

Discussion

The findings on auscultation of the ductus arteriosus were comprehensively reviewed by Marquis.[6] He highlighted the fact that when surgical ligation became a practical procedure the clinical diagnosis of a ductus arteriosus was judged untenable in the absence of a continuous murmur.[7 8] Subsequent experience[9] showed that the classic continuous murmur was not always present. The murmur could be confined to systole, when it was characteristically a crescendo with late systolic accentuation. Most cases of an atypical murmur were associated with a very large ductal flow or pulmonary hypertension.[1 2] Rowe described a group of patients who presented with nonspecific murmurs, clinically not of ductal origin, and in whom invasive investigations showed a trivial duct[10]; these patients resemble the group that we studied.

We describe the identification of a ductus arteriosus by Doppler echocardiography in patients who were later reassessed by experienced cardiologists with the possibility of the diagnosis in mind; they could find no clinical evidence of a ductus arteriosus. The ultrasound detection of a silent ductus arteriosus is simple and this diagnosis will become increasingly common as sensitive Doppler echocardiographic techniques become more widely used. Before the introduction of Doppler techniques a ductus arteriosus would not have been recognised in these patients. Our patients came from a group who were referred for ultrasound studies for various reasons (table 2). Thirteen had been referred with an innocent murmur and in six no murmur was audible. In addition, ductal flow which could not be detected clinically was demonstrated in patients with other defects who were excluded because the murmur of the other lesion (such as aortic stenosis, coarctation of the aorta, or ventricular septal defect) was loud at the upper left sternal edge. The findings indicate that as many as 0·5% in those presenting with innocent murmurs may have a ductus arteriosus. Because our patients are from a selected group we cannot estimate the incidence of a ductus arteriosus in the general population. It is likely to be higher than that estimated by previous diagnostic methods (0·065%).[11]

Early reports of a high incidence of infective endocarditis in those with a ductus arteriosus[7 12] led to the view that closure is the appropriate treatment. Should this recommendation apply to a ductus arteriosus that is so small that it evades clinical detection? The patient is certainly not at risk from pulmonary vascular disease or cardiac failure and the only possibility that needs to be considered is infective endocarditis. If the incidence of infective endocarditis in those with a clinically apparent duct (40%)[7 12] was found in those with a silent duct it seems likely that the association would have been recognised before now. However, it is possible that patients considered to have infective endocarditis in a normal heart may have a minor abnormality such as a tiny duct. At present we do not recommend either closure or antibiotic prophylaxis; but further experience may modify our policy. We explain the nature of the lesion to patients or parents and stop routine follow up examinations. We maintain a register of their names so that if opinion changes they can be recalled.

Two patients in our group had previously undergone surgical ligation of a duct. In one patient no murmur was audible and in the other only the murmur of mitral valve prolapse was present. However, Doppler ultrasonography identified a tiny residual ductal flow in both. There have recently been reports of the finding of tiny, clinically inaudible residual leaks detectable only by detailed Doppler ultrasound in some patients who had undergone transcatheter umbrella occlusion of a ductus arteriosus.[13 14] But it should be borne in mind that clinically undetectable trivial residual flow may occur after surgical ligation as shown in two of our patients.

Doppler ultrasonography can identify previously unrecognised features of the pattern of blood flow in the heart and vessels. Some of these may be the apparently normal finding of physiological valve regurgitation[15] and others a minor abnormality such as the silent ductus arteriosus. Do patients with a silent ductus arteriosus require prophylaxis against infective endocarditis? Doppler ultrasound examination of patients with infective endocarditis but without clinically recognisable antecedent heart disease and long term prospective studies may establish the place of antibiotic prophylaxis.

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Br Heart J 1991;**65**:100–1

CASE REPORTS

Fatal aortic rupture during balloon dilatation of recoarctation

Seshadri Balaji, Rachel Oommen, Philip G Rees

Abstract

In an eight year old boy with a patch aortoplasty, the aorta ruptured during balloon angioplasty for recoarctation. At necropsy a 1·5 cm long, full thickness tear and a separate, smaller, intimal tear were found. Histological examination showed thinning of the elastic laminae of the aorta.

Angioplasty for recoarctation may be dangerous in patients with a patch aortoplasty.

Balloon angioplasty is now an accepted method for the relief of recoarctation of the aorta.[1 2] There are six reports of death after this procedure.[1 2] Cooper *et al*, from our hospital, reported successful balloon angioplasty with no mortality in 46 patients.[3] We report a case of fatal aortic rupture after balloon angioplasty by the same technique as reported by Cooper *et al*.[3]

Case report

We performed balloon angioplasty for recoarctation in an eight year old symptom free child. He had undergone resection and end to end anastomosis at the age of 12 days, followed by patch aortoplasty for recoarctation at the age of five months, and closure of ostium primum atrial septal defect when he was four years old. He had persistent upper limb hypertension controlled by enalapril, poor femoral pulses, and evidence of left ventricular hypertrophy on the electrocardiogram and the echocardiogram. Doppler examination of his descending aorta showed an instantaneous gradient of 36 mm Hg with flow extension to diastole typical of a coarctation. At catheterisation a peak to peak gradient of 20 mm Hg was found and angiography showed two indentations on the inner curve of the aorta just distal to the left subclavian artery (fig 1).

We used angiographic methods described elsewhere[3] to measure the diameter (14 mm) of the aorta immediately proximal to the coarctation. Balloon dilatation was performed initially with a 15 mm diameter and 3 cm long balloon (Meditech). We did not use manometry to determine balloon pressure because we had found that it was usually not possible to overinflate a balloon to a diameter greater than its manufactured one. On the second inflation the balloon burst. Repeat angiography showed that the recoarctation was unchanged. A 12 mm diameter, 4 cm long balloon (Olbert Catheter System) was re-sited across the coarctation with the same guide wire and inflated twice. During the deflation phase after the second inflation there was sudden opacification of the upper lobe of the left lung, blood came from the endotracheal tube, and blood pressure fell. A full resuscitation procedure was instituted and an emergency left thoracotomy carried out; haemostasis was achieved with difficulty. Despite vigorous attempts at resuscitation the child deteriorated and he died 4 hours after the procedure.

At necropsy there was a longitudinal tear (1·5 cm) in the aorta adjacent to the patch. It extended through all layers (fig 2). The upper lobe of the left lung was wrapped around the aorta with dense adhesions. There was a

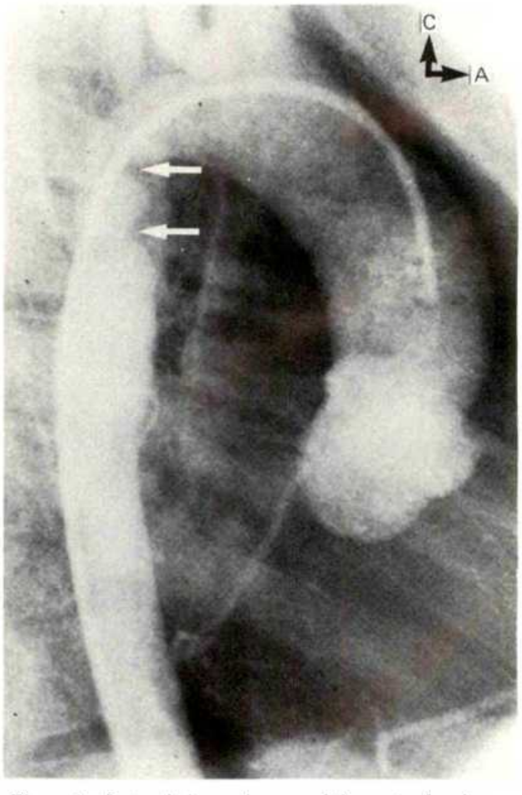

Figure 1 Lateral cineangiogram of the aorta showing two discrete areas of stenosis (arrows). A, anterior; C, cranial.

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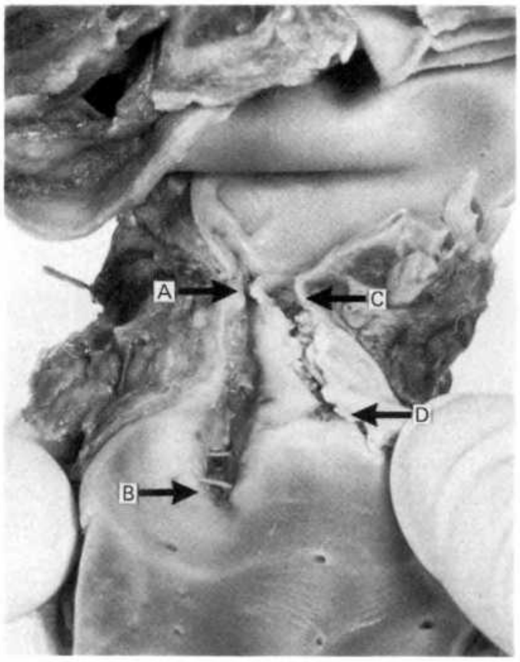

Figure 2 Appearance of the aortic wall after death (seen from the intimal surface). There was a full thickness through the aortic wall (A–B), and a separate intimal tear (C–D).

separate intimal tear (0·5 cm long) opposite the patch (fig 2).

Discussion

Balloon angioplasty has been hailed as a major advance in the treatment of recoarctation of the aorta.[4] Six deaths have been reported after this procedure. Kan *et al* reported one death that was thought to be due to a vagal event.[1] Hellenbrand *et al* recently reported the results of the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) registry. There were five deaths in a group of 200 patients undergoing balloon angioplasty for recoarctation.[2] Of these, only one was due to aortic rupture. Hellenbrand *et al* did not report the initial surgery undergone by this patient.

The Boston group (J E Lock, personal communication) have performed balloon angioplasty on 32 patients after patch aortoplasty with no complications. They have suggested to us that when the initial balloon burst it produced aortic damage because of the sudden release of shear forces and that the subsequent inflations enlarged the tear and resulted in rupture.

If the aorta ruptures we believe that the balloon should be reinflated across the ruptured segment and surgical repair started immediately. More experience of the effects of angioplasty is likely to identify specific subgroups in which balloon angioplasty is hazardous. We did not think that patch aortoplasty was a contraindication to balloon angioplasty and we had already achieved good results in four patients.[3]

Until more is known about the results of balloon angioplasty for aortic recoarctation we propose that this procedure should be avoided in patients with patch aortoplasty. We believe that further inflations should be avoided after a balloon has burst across an area where the vessel wall is likely to be thinned.

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Br Heart J 1991;**65**:102–3

Fatal pneumococcal septicaemia associated with asplenia and isomerism of the right atrial appendages

I A Murdoch, R Dos Anjos, A Mitchell

Abstract

A 22 month old male infant with isomerism of the right atrial appendages (associated with a complete atrioventricular septal defect, double outlet right ventricle, and pulmonary valve stenosis) died from pneumococcal septicaemia after a 36 hour illness. He had not been given penicillin prophylaxis. Asplenia was confirmed at necropsy.

In a survey of 50 paediatric cardiologists in the United Kingdom, 13 (33%) of the 40 (80%) who replied did not advise any prophylactic measures against pneumococcal infection in patients with isomerism of the right atrial appendages.

Isomerism of the right atrial appendages is usually found in association with severe forms of cyanotic congenital heart disease.[1] It is almost always associated with asplenia.[2] This may predispose the child to infection by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.[3]

Daily prophylactic penicillin and vaccination with a pneumococcal vaccine (Pneumovax) have both been shown to reduce the incidence of pneumococcal infection in patients with asplenia.[4 5]

We report this case to highlight the continued need for awareness of the increased infection risk in children with isomerism of the right atrial appendages. This case also prompted us to send a questionnaire to 50 paediatric cardiologists in the United Kingdom to see what were their current recommendations for prophylaxis in children with this type of defect. Forty (80%) replied and the results are reported.

Case report

A male infant was noted to be cyanosed at birth. Having failed a hyperoxia test he was transferred for cardiac assessment when he was one day old.

Physical examination showed a cyanosed infant weighing 4·0 kg with a 3/6 ejection systolic murmur that was loudest at the second left intercostal space. An echocardiogram showed isomerism of the right atrial appendages. The pulmonary veins drained to the left sided atrium. There was a complete atrioventricular septal defect with a double outlet right ventricle. In addition, there was pulmonary valve stenosis with a Doppler estimated gradient of 36 mm Hg.

His cyanosis worsened and when he was 10 days old a modified right Blalock-Taussig shunt was constructed with a 5 mm polytetrafluroethylene (Gore-tex) graft. The postoperative course was uneventful. He was discharged. He remained well and continued to thrive. No prophylactic penicillin was advised.

When he was 22 months old, after a short 6 hour febrile illness he became lethargic and stuporose. He was admitted to the local hospital where a full screen, including a lumbar puncture and a urine screen for pneumococcal antigens, was performed.

Treatment with intravenous benzylpenicillin (50 mg/kg four hourly) and gentamicin (3 mg/kg eight hourly) was started. Six hours later there was further deterioration in his level of consciousness and he was transferred to the regional paediatric intensive care unit.

On arrival he was hypotensive with a systolic blood pressure of 50 mm Hg and with a temperature gap of 10°C between the core and periphery. He was given colloid and treatment with dobutamine (10 μg/kg/min) and dopamine (3 μg/kg/min) was started. Initial haematological investigations showed a normal white cell count ($6 \cdot 7 \times 10^9$/l and evidence of disseminated intravascular coagulation.

Echocardiography showed that the Blalock-Taussig shunt was patent and no intracardiac vegetations were seen. Ventricular function was also normal. Blood cultures taken at the local hospital isolated *Streptococcus pneumoniae* at 24 hours; the organism was fully sensitive to penicillin.

Despite treatment, bradycardia and hypotension developed after 36 hours of illness and he died. At necropsy no vegetations were seen in either the heart or on the shunt and no splenic tissue was found.

Results of survey

Forty (80%) paediatric cardiologists responded to the survey. Half of the respondents recommended daily penicillin and pneumococcal vaccination in children with isomerism of the right atrial appendages. Four (10%) recommended penicillin alone and three (7%) recommended only pneumococcal vaccination. Thirteen (33%) recommended neither.

Twenty one of the 24 (60%) who recommended penicillin prophylaxis would have started it at the time of diagnosis. Three consultants would have waited until the child was 6–12 months old before starting prophylaxis. Twenty two recommended its indefinite use,

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one suggested stopping it at eight years of age, and the other immediately after pneumococcal vaccination, which was at three years of age in their unit.

Twenty three (57%) recommended pneumococcal vaccination as part of their prophylaxis policy, and 20 would have combined it with penicillin. One would have stopped penicillin on vaccination and two recommended pneumococcal vaccination alone. The timing of the pneumococcal vaccination was variable. About half (12 paediatric cardiologists) suggested vaccination at two years of age, two (10%) at three years, two (10%) at some time between the age of six to twelve months, and the remaining seven (30%) left it to the discretion of the local paediatrician. One consultant also recommended that the *Haemophilus influenzae* and meningicoccal vaccines should also be given.

Discussion

About 1% of infants with congenital heart disease have isomerism of the right atrial appendages.[1] In life this is usually diagnosed when echocardiography shows that the aorta and inferior vena cava are positioned on the same side of the spine.[6]

Isomerism of the right atrial appendages is almost always associated with asplenia.[2] A review of 52 patients with asplenia and congenital heart disease by Waldman *et al* showed that most died of their associated congenital heart defect in the first year, usually in the first month; after this period the commonest cause of death was infection.[7] As surgical techniques improve, more children with isomerism of the right atrial appendages may survive longer and the risk of overwhelming infection will be high.[3]

Recent publications of guidelines for the use of pneumococcal vaccination[8 9] have highlighted the importance of prophylaxis against pneumococcal infection in patients with functional asplenia and those undergoing splenectomy, in whom prophylactic penicillin is already known to reduce the incidence of pneumococcal infection.[4] But no attention has been paid to patients with asplenia associated with isomerism of the right atrial appendages. This is clearly reflected by a variable policy of recommendations by the paediatric cardiologists in the United Kingdom.

We believe that these guidelines are as applicable to children with isomerism of the right atrial appendages. At diagnosis daily penicillin prophylaxis should be started and continued indefinitely. The child should also be vaccinated at the age of two with Pneumovax II, and this should be repeated indefinitely every 6 years. Finally, the importance of the susceptibility of these patients to life threatening infection should be emphasised to the child's parents, general practitioner, and general paediatrician.

We thank Dr S A Qureshi for his help in the preparation of this report

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Familial aneurysms of the interventricular septum

Ming-Ren Chen, Michael L Rigby, Andrew N Redington

Abstract

Congenital aneurysms of the interventricular septum were found in a 29 year old man and his four year old son. Both were symptom free. In both, M mode and cross sectional echocardiography showed an aneurysm in the mid-muscular trabecular portion of the ventricular septum with considerable paradoxical motion of the aneurysmal segment. Otherwise the chamber dimensions, intracardiac structures, and cardiac function were normal for age.

Congenital aneurysm of the interventricular septum is rare and these familial cases may be unique.

Most left ventricular aneurysms occur in adults and are related to coronary occlusion and myocardial ischaemia. In childhood the acquired causes of left ventricular aneurysm include anomalous origin of the left coronary artery from the pulmonary artery, transient myocardial ischaemia of the newborn, blunt trauma to the chest, infection (syphilis, tuberculosis, rheumatic fever, mycosis, Chagas's disease, myocarditis), postoperative cardiac surgery, cardiomyopathies, sarcoidosis, and Kawasaki disease.[1] Congenital left ventricular aneurysm, which usually affects the annular subvalvar portion of the free wall or apex, is rare but well described.[1-3] Congenital aneurysms of the interventricular septum are most unusual and only two cases have been reported.[4 5] We report two further cases occurring in a father and his child. To our knowledge, familial, congenital aneurysm of the interventricular muscular septum has not been reported before.

Case report

A four year old boy was referred for cardiac evaluation. He was symptom free, with no relevant past medical history. On examination he was pink with normal parasternal impulses and normal peripheral pulses. The first and

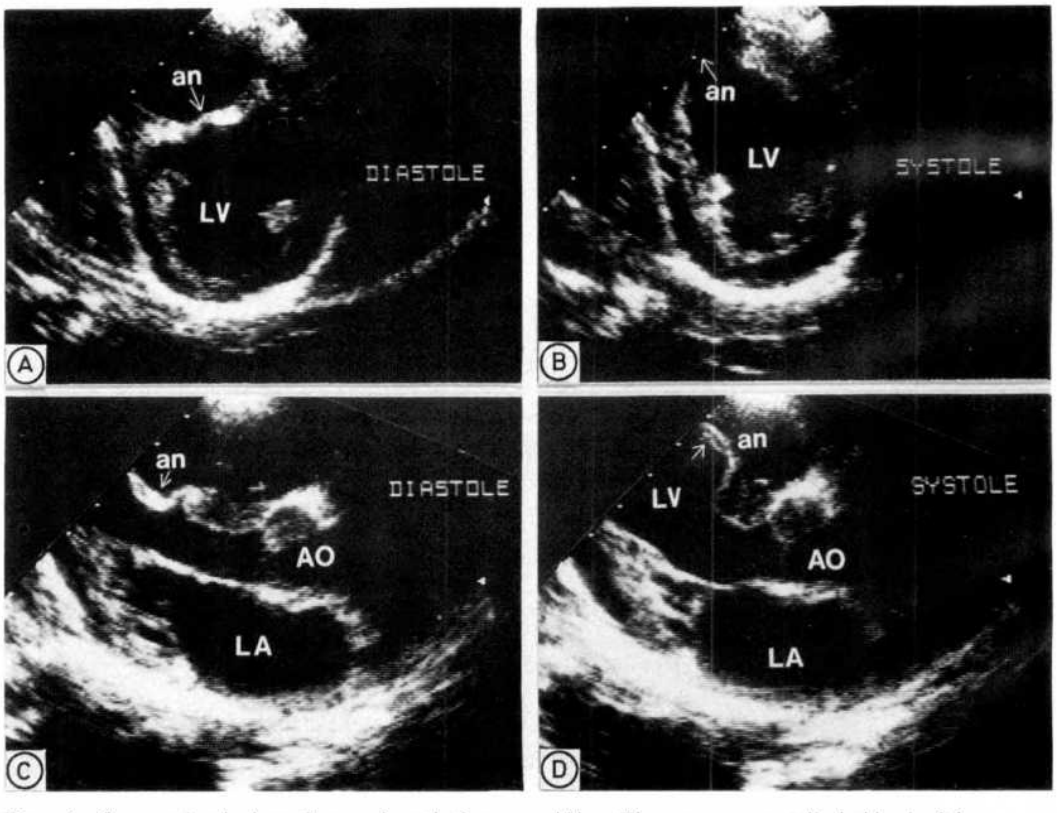

Figure 1 Cross sectional echocardiogram from the four year old boy. There was gross systolic dyskinesis of the aneurysmal segment of the interventricular septum in the parasternal short axis (A and B) and long axis (C and D) sections. Note the clear demarcation between normal myocardium and the aneurysmal segment. LV, left ventricle; LA, left atrium; AO, aorta; an, aneurysm.

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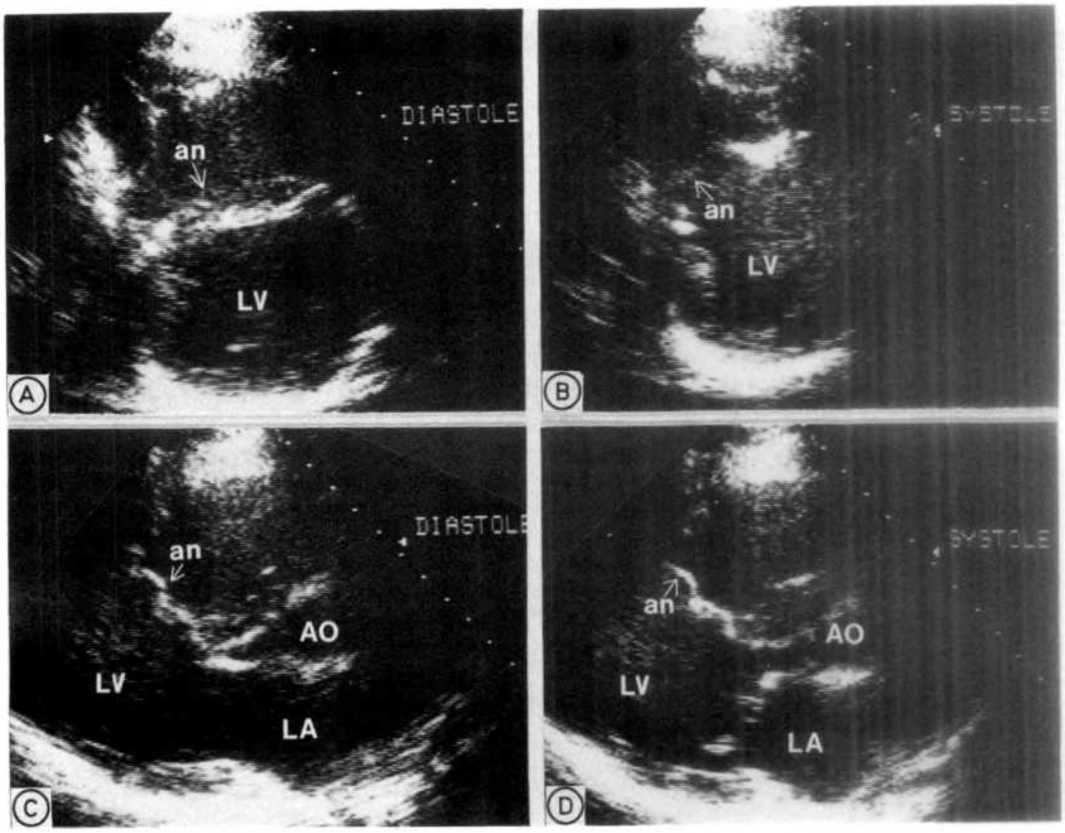

Figure 2 Cross sectional echocardiograms from the father of the four year old boy. There was a similar aneurysmal area in the mid-muscular portion of the interventricular septum. The amplitude of dyskinetic motion of the aneurysmal segment was not as large as in his son (fig 1).

second heart sounds were normal but there was a loud mid-systolic ejection click. There were no murmurs, and no other abnormalities were detected.

Chest radiography was normal. The electrocardiogram showed sinus rhythm, with a mean frontal QRS axis of +20 and a normal adult precordial RS progression pattern. There were no Q waves but the T wave was inverted in V5 and biphasic in V6. Cross sectional echocardiography confirmed atrial situs solitus with normal atrioventricular and ventriculoarterial connections. There was a large area of paradoxical systolic motion in the mid-muscular trabecular interventricular septum. The demarcation between myocardium and the aneurysmal segment was clear (fig 1). The phonocardiogram confirmed a systolic ejection click that did not coincide exactly with the anterior movement of the aneurysm recorded with M mode echocardiography.

The child's father also underwent echocardiographic examination because of an earlier investigation for congenital heart disease. No previous records were available. He was 29 years old and symptom free. There was no relevant past history. The chest radiograph, electrocardiogram, and physical examination were normal. M mode and cross sectional echocardiography showed a similar aneurysm in the mid-muscular part of the interventricular septum (fig 2). Again, there was obvious demarcation between the normal myocardium of the interventricular septum and the aneurysmal segment.

Discussion

This paper describes the familial occurrence of congenital aneurysms of the muscular interventricular septum. Only two cases of congenital aneurysm of the interventricular muscular septum have been reported before. In one, a 15 year old girl presenting with exertional dyspnoea, it was associated with a secundum atrial septal defect, a cleft mitral valve, and symptomatic ventricular tachycardia.[4] There was extensive fibroelastosis of the right ventricle. This patient underwent surgery with suture of the mitral valve cleft and patch closure of the atrial septal defect. Aneurysmectomy was not considered possible. The other case was a symptom free 10 year old girl with clinical signs of a small ventricular septal defect.[5] The electrocardiogram in this patient showed Q waves in the septal leads. The aneurysm was shown by cross sectional echocardiography. Furthermore, there was rupture of the aneurysm in the mid-portion of the interventricular septum, accounting for the clinical signs of a ventricular septal defect. The echocardiographic appearances in our patients were remarkably similar to those reported before—with a large area of well demarcated aneurysmal interventricular muscular septum towards the apex of the left ventricle. Neither of our patients had fibroelastosis of the ventricles or rupture of the aneurysm.

The cause of these aneurysms is unknown. The familial occurrence in our patients may support the concept that they may result from an inherited embryological defect leading to weakness of the myocardium.[6] We suggest that all first degree relatives of affected patients be screened by cross sectional echocardiography, particularly if there is an abnormal electrocardiogram. A systolic ejection click should also suggest the possibility of a congenital ventricular aneurysm, but is by no means a universal finding.

The course of congenital ventricular aneurysm is not known. In these patients, as with other congenital aneurysms, complications are likely to include rupture, arrhythmia, thromboembolism, and deteriorating ventricular function.[3 6-8] The place for surgical treatment in these patients with uncomplicated lesions must remain uncertain, however. Surgical repair will be particularly difficult when a large part of the interventricular septum is affected,[4] and it is not clear whether the course would be influenced in the symptom free patient.

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Successful operation on a coronary arteriovenous fistula in a 74 year old woman

M J Brack, P J B Hubner, R K Firmin

Abstract

Coronary arteriovenous fistulas are rare and are usually diagnosed in children or young adults. Most are believed to be congenital. A right coronary arteriovenous fistula was first diagnosed in a patient of 74. Despite her age the fistula was successfully operated on and her symptoms were relieved.

Coronary arteriovenous fistulas are rare and are usually diagnosed in children or young adults.[1] Most occur as congenital anomalies but acquired fistulas may arise after thoracic trauma.[2 3] The right coronary artery is most commonly affected, and it usually communicates with the right heart chambers or the pulmonary artery.[4] In most instances the fistulas are small with insignificant shunts. This group of patients often remain symptom free. However, in the presence of larger shunts, congestive cardiac failure can occur, especially in the young or elderly.[5]

Case report

A 74 year old woman was referred in 1987 with a 7 year history of progressive dyspnoea and a one year history of paroxysmal nocturnal dyspnoea. She was considerably limited by her dyspnoea. In 1984 she presented to another hospital with mitral regurgitation and fever. She was treated for suspected infective endocarditis though no organism was isolated by culture. On follow up she continued to have a pansystolic murmur and the diagnosis was one of mitral regurgitation. She was referred for possible mitral valve replacement. In the past she had had a subtotal thyroidectomy for a thyroid adenoma. Her daily medication was digoxin 125 μg, frusemide 120 mg, amiloride 15 mg, and thyroxine 100 μg.

She was a sprightly woman of lean build. She was in atrial fibrillation (96 beats/minute) with a blood pressure of 150/90 mm Hg. The jugular venous pressure was raised to 4 cm. There was clinical left and right ventricular enlargement. On auscultation the striking finding, not previously reported, was of a loud continuous murmur heard in the aortic area that radiated to the lower right sternal edge. At the mitral area there was a moderately loud pansystolic murmur referred to the left axilla. There was no peripheral oedema and the lung fields were clear.

The electrocardiogram showed atrial fibrillation, an axis of 0°, and incomplete right bundle branch block. The chest *x* ray showed an enlarged heart (cardiothoracic ratio 70%). Cross sectional and M mode echocardiography showed normal mitral and aortic valves. The left ventricle was of normal size with normal contraction. Doppler echocardiography confirmed mitral regurgitation and no other abnormal flow patterns were detected.

Cardiac catheterisation was performed. Systolic and diastolic pressures were: right atrium 16/6 mm Hg, right ventricle 30/12 mm Hg, pulmonary artery 32/12 mm Hg, pulmonary capillary vein 18/10 mm Hg, aorta 120/60 mm Hg, left ventricle 120/10 mm Hg. There was a step up in oxygen saturation at the level of the right ventricle and the following oxygen saturations were recorded: aorta 95%, inferior vena cava 63%, superior vena cava 56%, right atrium 65%, right ventricle 68%, pulmonary artery 74%. The pulmonary to systemic flow ratio was 1·7:1. The left ventricular angiogram showed a normal sized left ventricle with good contraction. There was mild to moderate mitral regurgitation. Aortography showed a normal aortic valve ring with mild dilatation of the aorta above it. There was no aortic regurgitation. The right coronary artery was very large and tortuous, approximately three times the normal calibre (fig 1). Contrast passed from the right coronary artery via a fistula into an aneurysmal coronary sinus (fig 2). The left coronary artery was also abnormal, being dilated and tortuous with contrast passing via the distal left anterior descending artery to the area of the fistula.

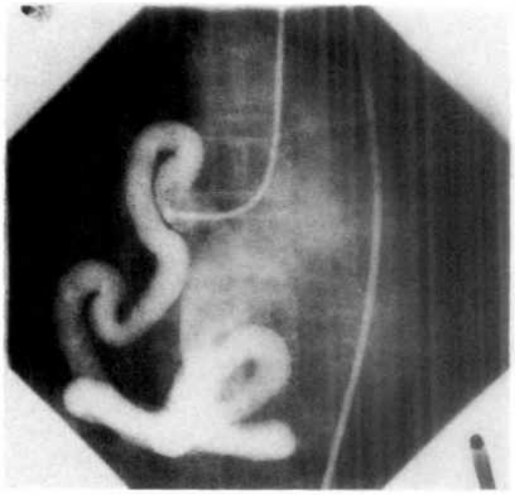

Figure 1 Right coronary angiogram showing a dilated tortuous vessel.

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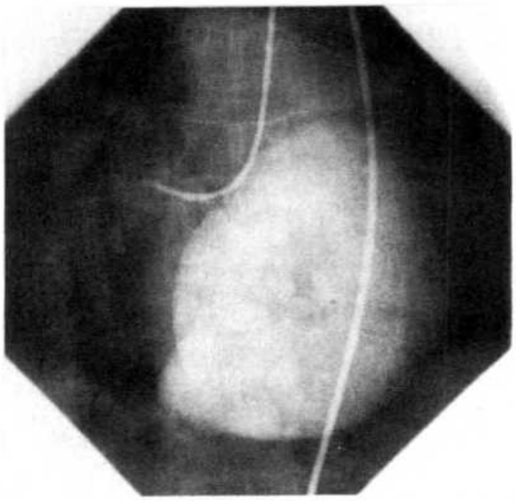

Figure 2 A late film showing contrast in aneurysmal coronary sinus.

Because she was considerably limited by her symptoms she was accepted for surgery. At operation a very dilated right coronary artery was opened distally showing a single 1 cm fistula opening into an aneurysmal coronary sinus. This area was obliterated with 5/O prolene stitches and then the coronary artery was double tied proximal to the stitched area. The distal right coronary artery was of small calibre. The mitral valve seemed normal. Her postoperative recovery was uneventful. The patient subsequently became symptom free. She no longer had a continuous murmur, nor one of mitral regurgitation. Repeat angiography a year after operation showed a dilated right coronary artery with no evidence of a fistula. There was collateral filling of the distal right coronary artery from the left anterior descending artery. Left ventricular angiography showed good left ventricular function with mild mitral regurgitation only. There was no evidence of any intracardiac shunt.

Discussion

In our patient the left to right shunt was not large (Q_p:Q_s 1·7:1), but her dyspnoea completely cleared when the fistula was closed. The dyspnoea was caused by a combination of a left to right shunt, mitral regurgitation, and atrial fibrillation. After operation the mitral regurgitation was also reduced. The reason for this is not clear because the left ventricular function was good, both before and after closure. Harris *et al* described a patient with normal resting right heart pressures and left ventricular end diastolic pressure.[4] The pulmonary wedge pressure rose from 6 to 32 mm Hg on exercise, suggesting reversible impairment of left ventricular function.

The prognosis in patients with coronary arteriovenous fistulas depends upon the volume of the shunt, the age of the patient, and the presence of any complications. The abnormality, however, is known to be compatible with a long life.[1] Though there is a risk of endocarditis, pulmonary hypertension, and rupture of the fistulas the risks are small and not an indication for operation.[6] In younger patients it is likely that elective ligation of arteriovenous fistulas may reduce the incidence of late complications.[7] There are also reports of spontaneous closure of arteriovenous fistulas.[8 9] In the presence of larger shunts or severe symptoms, however, surgical closure of the fistula is valuable but may be difficult especially if there are multiple communications.[5] For secure closure of the fistula in our patient the artery was ligated and obliterated at the site of the fistulous communication. The calibre of the distal right coronary artery was small. Vein grafting was considered but not performed because there was good filling of the right coronary artery from the abnormal circulation of the distal left anterior descending artery.

Though the risks of operation are increased in older patients age should not preclude operation. The results were very successful in our 74 year old patient.

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PRACTICE REVIEWED

Early complications of interventional balloon catheterisation in infants and children

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Abstract

Interventional balloon catheterisation is now the recommended procedure for several congenital heart defects. The overall complication rate in the first 160 children (median age 3 years) to undergo balloon intervention (excluding balloon atrial septostomy) at the Brompton Hospital was 24% (14% excluding haemorrhage and including three deaths (1·9%)). Most complications were related to vascular problems at the site of cardiac catheterisation. Complications were more common in the younger patient, especially neonates, and also in procedures that were ultimately unsuccessful. Most complications were transient and usually had no long term effects. Improvements in equipment design and technical expertise may reduce morbidity from these procedures.

The immediate and intermediate results of balloon dilatation for isolated pulmonary valve stenosis and for recoarctation of the aorta compare favourably with the results of conventional surgery.[1-3] The successful dilatation of aortic valve stenosis,[4-6] of native coarctation of the aorta,[7] of postoperative stenoses of veins or baffles,[8] and of stenosed aortopulmonary shunts has been reported but the longer term outcome of these procedures is unknown.

It is surprising that there is only one report of the acute complications of interventional catheterisation in adults and children.[9] The present study reviews the complications in children and represents our initial experience in the first 160 patients.

Patients and methods

Between January 1984 and June 1989, 1795 infants and children under the age of 16 years underwent cardiac catheterisation at the Brompton Hospital. There were 172 patients who underwent interventional procedures, consisting of balloon dilatation (n = 160), embolisation of pulmonary-systemic collaterals (n = 10), and blade atrial septostomy in two. Infants undergoing balloon atrial septostomy are not included. This study is confined to the 160 children who underwent balloon dilatation. Figure 1 shows the relative frequency of these procedures as a proportion of all cardiac catheterisations by year. Age at catheterisation ranged from 3 days to 16 years (median 3 years). There were 10 neonates (6·3%), 16 infants (10%), and 134 children (83·7%). Seven patients had repeat procedures. One hundred and nineteen (75%) procedures were considered to be successful on clinical, angiographic, and haemodynamic criteria. A procedure was considered unsuccessful if: (*a*) it was technically impossible; (*b*) there was less than a 50% reduction in the peak systolic gradient across a stenosis; (*c*) the patient required conventional surgery after balloon intervention. Otherwise the intervention was regarded as an early success. Table 1 lists the procedures undertaken and their individual success rate. All the procedures were performed by or under the supervision of one of four operators.

All balloon dilatation procedures were performed by standard techniques. In general, direct percutaneous insertion of the balloon catheter was used, except in some neonates undergoing balloon dilatation of aortic coarctation or critical pulmonary stenosis, when the balloon catheter was inserted via a valved introducer. Balloon size was selected according to previously published criteria.[10-12] The balloon diameter for dilatation of post-Mustard baffle obstruction and dilatation of the

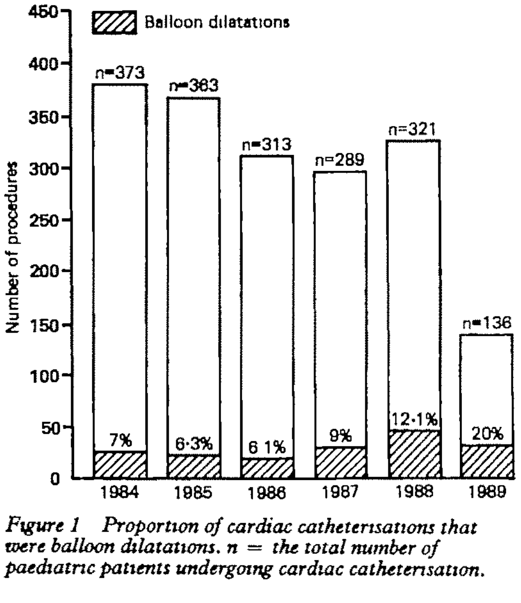

Figure 1 Proportion of cardiac catheterisations that were balloon dilatations. n = the total number of paediatric patients undergoing cardiac catheterisation.

Table 1 Procedures undertaken and their individual success rate

Procedure	*Total*	*Successful (n(%))*
Dilatation of pulmonary valve stenosis	81	70 (86)
Dilatation of aortic valve stenosis	12	5 (42)
Dilatation of aortic coarctation:	34	28 (82)
Native coarctation	16	15 (93)
Recoarctation	18	13 (72)
Dilatation of stenoses after Mustard's operation	12	10 (83)
Miscellaneous:	21	6 (29)
Dilatation of stenoses after arterial switch operation	9	
Dilatation of pulmonary artery stenosis	4	
Dilatation of stenosis after truncus repair	2	
Dilatation of stenoses after DORV and VSD repair	2	
Dilatation of stenosis after PA correction	1	
Dilatation of stenosis after correction of TOF	1	
Dilatation of mitral valve stenosis	1	
Dilatation of supravalvar pulmonary stenosis (Noonan's)	1	

DORV, double outlet right ventricle; PA, pulmonary atresia; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

pulmonary valve did not exceed 150% of the vein size or the valve ring respectively. For dilatation of the arterial tree, the balloon size was 80–100% of the size of the vessel or valve being dilated. All patients in the latter group received 50 IU/kg of heparin during the catheter procedure, followed by a heparin infusion at a dose of 400 IU/kg/24 hours. This was started as soon as haemostasis was achieved after the procedure.

COMPLICATIONS

Acute complications were classified as major (table 2) and minor (table 3). Complications were considered to be major if: (*a*) the patient died or was admitted to the intensive care unit after the procedure; (*b*) immediate surgical intervention was required; (*c*) permanent damage was caused to any other organ or system; (*d*) there was haemorrhage that required an immediate blood transfusion because of haemodynamic disturbance.

Minor complications included: transient loss of pulse distal to the catheter insertion site, transient pallor and hypothermia of the limb, the administration of anticoagulant treatment for longer than 24 hours, and blood loss requiring elective blood transfusion.

As expected during valve dilatation there was a transient fall in systemic pressure, bradycardia, and occasional ventricular extrasystoles during balloon inflation but these were not regarded as complications.

Results

There were 48 complications in 39 patients (24%), of which 27 were major and 21 minor.

Table 2 Major complications after balloon dilatation procedures

Complication	*No*
Haemorrhage and hypotension	10
Femoral artery occlusion	3
Ventricular fibrillation	2 (2 died)
Hemiparesis/hemiplegia	2
Cardiac arrest	1
Perforation of right ventricular outflow tract	1 (died)
Complete heart block	1
Aortic regurgitation	1
Lower limb ischaemia	1
Ruptured catheter	1
Aortic dissection	1
Aortic aneurysm	1
Air in left atrial appendage	1
Septicaemia and valvar endocarditis	1

Table 3 Minor complications after balloon dilatation procedures

Complication	*No*
Transient loss of pulse	10
Haemorrhage and transfusion	7
Damage to axillary artery	1
Venous occlusion	1
Erb's palsy	1
Pulmonary artery puncture, no haemorrhage	1

There were three deaths (1·9%) (tables 2 and 3). Seven patients had two complications and one patient had three. The complication rates for individual procedures ranged from 7% for dilatation of the pulmonary valve to 53% for coarctation aortoplasty (fig 2). The complication rate was especially high (69%) for aortoplasty of native coarctation.

Complications were more common in the younger patients. The rate was 70% for neonates, 44% for infants, and 19% for children ($p < 0{\cdot}001$, χ^2 test for trend). The median age of the patients in whom complications developed was 24 months; the median age of the patients who had no complications was 43 months. The difference between the median ages was significant ($p = 0{\cdot}009$, Mann-Whitney U test). The 95% confidence interval for the difference in medians was (4·0 to 27·8). Complications developed in 18 (15%) of the 119 patients who had successful procedures and in 21 (51%) of the 41 patients who had an unsuccessful procedure ($p < 0{\cdot}001$, χ^2 test with Yates's correction).

During the period of the study the incidence of complications increased from 17·5% in the first 30 months to 28% in the second, though the rate for dilatation of the pulmonary valve fell.

SPECIFIC PROCEDURES AND THEIR COMPLICATIONS

Dilatation of the pulmonary valve

The success rate (86%) was the highest of all the procedures and the complication rate (7%) the lowest. There was one death (in a 5 day old infant) and in a 10 day old infant with a severely dysplastic pulmonary valve *Staphylococcus*

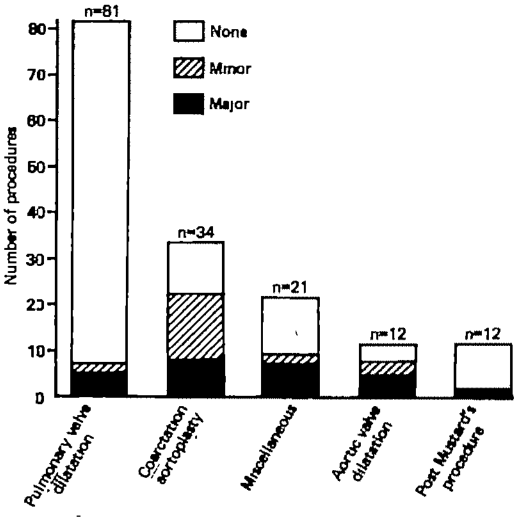

Figure 2 Complication rate by procedure. n = the number of patients in each group.

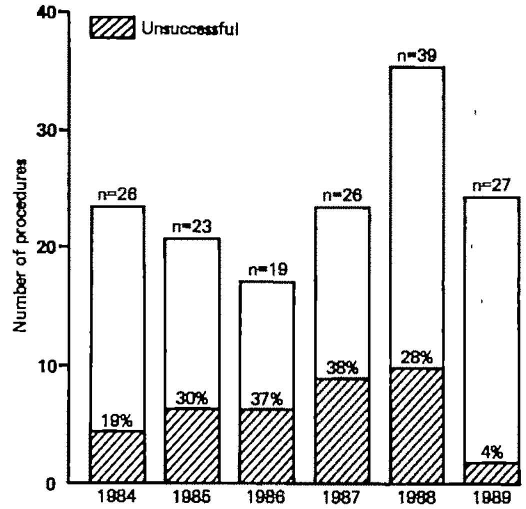

Figure 3 Success and failure rate of balloon intervention per year of procedure. n = the total number of balloon dilatations performed on paediatric patients.

aureus septicaemia developed after an unsuccessful procedure. At operation, two weeks later, endocarditis of the pulmonary valve and the arterial duct was noted together with a small pulmonary artery tear and a subadventitial haematoma. The child made an uneventful recovery after an open valvotomy and removal of the infected tissue. A 10 month old infant had a successful procedure but developed transient complete heart block necessitating admission to the intensive care unit. Three children had problems with bleeding at the site of cardiac catheterisation; two become hypotensive and required admission to the intensive care unit.

Dilatation of the aortic valve

The success rate of 42% was poor and the complication rate of 50% was high. Only one of the patients with complications had a successful procedure. There was one death, from late ventricular fibrillation. Two patients, aged 11 and 14 years, had persistent loss of pulse despite treatment with anticoagulant and antifibrinolytic agents. They both required surgical exploration of the femoral arteries; simple thrombectomy was performed in one, but in the other a saphenous patch was used. A six year old girl developed axillary artery thrombosis which resolved after five days of anticoagulation treatment. This same patient developed aortic incompetence and later underwent successful open valvotomy with repair of the valve. Finally, there were two patients with bleeding from the site of cardiac catheterisation. One required admission to the intensive care unit; the second also developed transient loss of pulse.

Coarctation aortoplasty

Thirty four patients underwent balloon aortoplasty. This group had a good initial success rate (82%) but the highest complication rate (53%). Eighteen of the procedures were performed in patients with recoarctation (14 after subclavian flap angioplasty, three after end-to-end anastomosis, and one after previous balloon aortoplasty). Primary balloon aortoplasty in 15 of 16 patients, including seven neonates, was initially successful. There were minor complications in 14 patients and major complications in eight. Four infants and an 18 month old child were admitted to the intensive care unit because of haemorrhage and hypotension or loss of pulse or both. All had successful procedures with no long term sequelae. One two week old infant had a successful aortoplasty but a small aneurysm was noted immediately. One three year old boy was noted to have a cold, pulseless right leg. Despite appropriate treatment intermittent claudication developed; magnetic resonance imaging showed stenosis of the right femoral artery. A three day old infant was admitted to the intensive care unit after unsuccessful balloon aortoplasty which was complicated by major blood loss. At operation, three days later, there was an aortic dissection of the coarctation and isthmus necessitating end-to-end repair. The minor complications involved nine patients with transient loss of pulse requiring anticoagulant treatment and four with bleeding from the site of cardiac catheterisation requiring blood transfusion but without haemodynamic disturbance.

Baffle obstruction after Mustard's operation

There were 12 procedures in 11 patients who had developed baffle obstruction. Eight underwent dilatation of the inferior limb of the baffle, three dilatation of the inferior and superior limb, and one the superior limb alone. The success rate of the procedures was high (83%) and the complication rate low (16%). One patient underwent two procedures for dilatation initially of the inferior limb and later of both limbs of the baffle. He developed a transient right hemiparesis on both occasions.

Miscellaneous

Table 1 lists procedures undertaken. The success rate was low (29%) and the complication rate was 33%. There was one death from ventricular fibrillation. A two year old child with Williams's syndrome and severe supravalvar aortic stenosis and peripheral pulmonary artery stenosis had repeated episodes of asystole after induction of general anaesthesia and during attempted dilatation of her pulmonary artery stenoses. She has recovered fully. Circumferential rupture of the balloon occurred in a 16 year old girl undergoing dilatation of a homograft conduit; it proved impossible to remove the catheter percutaneously and she required surgical exploration. Other complications included major haemorrhage with hypotension in one patient, transient loss of foot pulse in another, and venous thrombosis requiring anticoagulation in a third. All made a complete recovery. Finally, attempted dilatation of a supravalvar mitral ring in a two year old was unsuccessful and was complicated by minor haemorrhage. More importantly, fluoroscopy showed air in her left atrial appendage. She subsequently underwent surgical removal of the supravalvar ring with no long term sequelae.

DEATHS

There were three deaths. A five day old infant with severe aortic and pulmonary valve stenosis died from cardiac tamponade. A five month old infant who had undergone an arterial switch operation died 24 hours after unsuccessful attempted dilatation of critical stenosis of right and left pulmonary artery stenosis. Finally, spontaneous ventricular fibrillation developed two hours after balloon dilatation of the aortic valve in a six month old infant who had undergone open aortic valvotomy as a neonate.

Discussion

Complications developed in 39 (24%) of the first 160 infants and children undergoing balloon dilatation procedures. Permanent sequelae from these complications were uncommon, though there were three deaths (1·9%).

Unlike Fellows *et al*,[9] we included haemorrhage from the catheter site that required elective blood transfusion as a complication of balloon interventional procedures. If these 17 patients are excluded, the type and frequency (14%) of complications in our study are remarkably similar to those reported in Fellows *et al*'s review of adults and children. What is clear from both studies is that complications of balloon interventional catheterisation increase in frequency in the younger patient, especially neonates. We also showed that complications were more frequent in patients who had an unsuccessful procedure (fig 3), presumably because these were more prolonged and technically difficult. Vascular problems associated with site of cardiac catheterisation (haemorrhage, arterial occlusion etc) accounted for 33 of the complications. It seems reasonable to conclude that the frequency of these complications may fall with further miniaturisation of equipment.

Our success and low complication rates after dilatation of the pulmonary valve accord with those reported by other workers.[1 2 13] The complication rate (53%) for coarctation aortoplasty was the highest of all procedures. This was balanced by its high initial success rates of 82% overall and 94% for native coarctations. Fourteen were minor complications—that is, transient loss of the foot pulse or haemorrhage from the catheter site. There was a preponderance of neonates and infants in this group, and like Fellows *et al*[9] we have shown an increased complication rate in these patients. It is clear that an arterial approach and younger age are significantly associated with both minor and major complications. Indeed, the complication rate rose from 17·5% over the first 30 months of the study to 28% over the past 30 months. This almost certainly reflects the increasing number of neonates and infants being treated, the trend towards primary balloon aortoplasty for coarctation, and the relative reduction in frequency of dilatation of the pulmonary valve.

Several workers have reported deaths after balloon dilatation, especially for aortic stenosis, aortic coarctation, and pulmonary artery stenosis.[14-16] In general, the overall mortality is comparable to that of the surgical alternative. Deaths reported after balloon intervention have been due to ventricular fibrillation, vessel rupture, or occlusion of a critical obstruction. The deaths in our study were caused by perforation of the right ventricular outflow tract in one and later ventricular fibrillation in two patients. The exact cause of late arrhythmias is unknown, but it is now our policy to monitor the electrocardiogram continuously for 24 hours after most procedures.

We described a retrospective review of balloon interventional techniques in infants and children. Overall the early complication rate was high but the frequency of complications likely to lead to long term sequelae was low. With continued improvement in equipment and operator technique, many of these complications may be avoidable.

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11 Miller GAH. Balloon valvuloplasty and angioplasty in congenital heart disease *Br Heart J* 1986;54.285–9.

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15 Finley JP, Beaulieu RG, Nanton MA, Roy DL. Balloon catheter dilatation of coarctation of the aorta in young infants. *Br Heart J* 1983,50.411–5

16 Kasten-Sportes CH, Piechaud JF, Sidi D, *et al*. Percutaneous balloon valvuloplasty in neonates with critical aortic stenosis. *J Am Coll Cardiol* 1989,5.1101–5.

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Balloon dilatation of tricuspid stenosis caused by carcinoid heart disease

SIR,—Mullins *et al's* conclusion that balloon dilatation of the tricuspid valve is safe and effective for tricuspid stenosis caused by carcinoid may not be consistent with clinical and haemodynamic data in their patient (*Br Heart J* 1990;**63**:249–50). They state that the jugular venous pulse showed a prominent systolic wave. This clearly means that tricuspid regurgitation was a clinically important abnormality. This accords with the haemodynamic data because in the basal state the 'v' wave in the right atrium was 44 mg Hg whereas the 'a' wave was 24 mm Hg. They say that the chest *x* ray showed pulmonary oedema. This is an unusual and unlikely feature of primary tricuspid valve disease, especially when there is no additional left sided disease. Because there was no mention of myocardial or valve disease affecting the left heart I presume that these structures were normal.

Right ventricular hypertension in carcinoid heart disease affecting the right side of the heart is possible only if there is stenosis of the pulmonary valve The pulmonary valve was normal in this case, so what was the cause of the right ventricular pressure of 52 mm Hg? In addition, a right ventricular diastolic pressure of 18 mm Hg is rather surprising in the presence of important tricuspid stenosis without any additional cause for diastolic restriction of the right ventricle.

After dilatation of the tricuspid valve the 'a' wave in the right atrium remained at 24 m Hg whereas the height of the 'v' wave fell from 44 to 36 mm Hg This needs to be explained. Mullins *et al* claim that the severity of tricuspid regurgitation did not change after dilatation so what was the cause of reduction in the height of the 'v' wave?

Though after dilatation the mean pressure drop across the tricuspid valve fell from 10·5 to 7·6 mm Hg and the valve area increased from 0·9 to 1·4 cm², are Mullins *et al* justified in calling this dilatation "effective"? The reduction in the mean pressure drop could have been solely related to the reduction in the height of the 'v' wave, especially as the height of the 'a' wave was unchanged. Without knowledge of the cardiac output the effectiveness of dilatation cannot be judged solely on the values of the pressure drops. Though the area of the tricuspid valve increased, its absolute value of 1·4 cm² still indicates a critical tricuspid stenosis.[1]

What is more impressive is the fact that despite an 'a' wave of 24 and a 'v' wave of 36 mm Hg in the right atrium after balloon dilatation the "patient is doing well with reduction of dyspnoea and pulmonary and peripheral oedema". Why did the pulmonary oedema resolve after the release of the tricuspid stenosis?—when it seems logical to expect an increase in pulmonary oedema because of increased flow in the pulmonary circuit.

Unless these discrepancies are sorted out I cannot accept that this was predominantly a case of tricuspid stenosis requiring balloon dilatation. Moreover, on the basis of these data alone I believe that it is not correct to call this dilatation effective and recommend it for carcinoid valve disease.

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1 Kitchin A, Turner R. Diagnosis and treatment of tricuspid stenosis. *Br Heart J* 1964;26:354–79.

This letter was shown to the authors who reply as follows:

SIR,—We are grateful for Dr Dalvi's interest in the case we presented. He raises three points for debate.

Firstly, was there significant tricuspid stenosis? Tricuspid stenosis was confirmed by a transvalvar gradient of 10·5 mm Hg and an orifice area of 0·9 cm² estimated by Doppler echocardiography. The criticism that the presence of a cardiac catheter across the valve during the haemodynamic study leads to an overestimation of the gradient can be levelled at all gradient estimations. This criticism, however, is not valid when the orifice area is estimated by Doppler echocardiography at a different time and the method is not subject to the same measurement constraints.

Secondly, why did the patient have a raised right ventricular diastolic pressure and pulmonary oedema? These abnormalities are not a feature of pure tricuspid stenosis. This elderly woman, presenting with carcinoid, also had poor left ventricular function, the cause of which was not investigated further We postulated that fluid retention caused by tricuspid stenosis and poor ventricular function was responsible for the pulmonary congestion.

Thirdly, was the tricuspid dilatation successful? We showed a reduced mean gradient and an increase from 0·9 cm² to 1·4 cm² in orifice area estimated by Doppler echocardiography The patient's symptoms of fluid retention and dyspnoea rapidly improved. The increase in tricuspid valve orifice area was maintained on a later echocardiogram.

This patient was terminally ill and in a very poor clinical state. Our aim was to palliate the symptoms associated with her severe tricuspid valve disease. The small improvement in tricuspid valve orifice was sufficient for this purpose.

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Diagnosis of a pseudoaneurysm of the right ventricular outflow tract

SIR,—Sreeram *et al* reported the diagnosis of a pseudoaneurysm of the right ventricular outflow tract (1990;**63**:129–31) Their colour Doppler picture certainly shows clearly the narrow communication between the right ventricle and the pseudoaneurysm.

Those who do not have a colour Doppler machine may be interested to know that a communication such as this can also be detected by contrast echocardiography, as we reported a few years ago.[1]

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Israel

1 Garty BZ, Berant M, Weinhouse E, Levinski L False aneurysm of the right ventricle due to endocarditis in a child. *Pediatr Cardiol* 1987;8:275–7

This letter was shown to the author, who replies as follows:

SIR,—As Berant and Garty point out in their letter, the use of contrast echocardiography may be a valuable adjunct to the investigation of patients in whom a pseudoaneurysm of the right ventricular outflow tract is suspected.

While contrast echocardiography is a useful alternative non-invasive approach to diagnosis where colour flow mapping is not available, we suggest that colour flow mapping is a more appropriate technique because it can be quickly and easily carried out as part of the ultrasound examination itself. It does not require an intravenous line and administration of a contrast agent Furthermore, the contrast effect produced can be variable in such patients and thus the results of such studies could be misleading. We expect colour flow mapping will prove to be a more sensitive and specific technique.

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CORRECTION

Review. Late potentials as predictors of risk after thrombolytic treatment? *Günter Breithardt, Martin Borggrefe, Ulrich Karbenn* (September 1990 issue, volume 64: pages 174–6)—We regret that an editorial error was introduced into this article. Lines 9, 10, and 11 of the second paragraph on page 174 should have read: There was an inverse relation between the duration of late potentials and the rate of ventricular tachycardia.

BRITISH CARDIAC SOCIETY NEWSLETTER

We have received a total of 581 abstracts for the Glasgow meeting, a 29% increase compared with the number submitted for Torquay. Only a minority can be selected for presentation, but as many as possible of the remaining suitable abstracts will be accepted for posters. Those with the difficult task of selection are not endowed with any unique wisdom, and some posters may contain more valuable information than is available in many of the presentations Posters receive less attention than they deserve. What can be done to improve this? In their meetings the Irish Cardiac Society arrange for very brief summaries of salient information to be presented by the authors during one of the oral sessions, designed to whet the appetite. Two or three minutes of explanation can also greatly reduce the effort needed to master the printed word. Is it worth considering?

In August last year we raised the question of the initials FESC being used by those elected to the European Fellowship of Cardiology We think they should be, when it is appropriate to do so; but too few of the members of the British Cardiac Society have this distinction. The European Society states that "a Fellow is considered to be a person who has had a number of years of experience in the field and who has distinguished himself (sic) individually in clinical, educational, investigational, managerial or professional aspects of cardiology . . . Each applicant should be sponsored and signed by two leading cardiovascular specialists or scientists, one of whom must be the President of the National Cardiac Society." The council of the British Cardiac Society believes that only those who have achieved consultant status should have names put forward at the present time. But why have so few decided to do so? Many have the appropriate credentials. The address of the Secretariat is ESC Fellowship Department, 22 Rue Juste Olivier, CH-1260 Nyon, Switzerland.

We have news from the European Resuscitation Council. This multidisciplinary group has representatives from, among others, the European Society of Cardiology, the European Academy of Anaesthesiology, the European Society for Intensive Care Medicine, and all the appropriate national societies. A group from the council met in December with delegates from the American Heart Association, the Heart and Stroke Foundation of Canada, and the Australian Heart Foundation. The purpose was to agree on the terminology of resuscitation and for enough uniformity in the methods of reporting results to permit comparison of data. This is rarely possible at present. The joint chairmen were Richard Cummins of Seattle and Douglas Chamberlain from Brighton. At times the differences in even simple definitions between the continents seemed surprising. But with abundant goodwill on all sides the differences were speedily resolved. The outcome will be reported in due course, probably with near simultaneous publications on the two sides of the Atlantic. The European Resuscitation Council has reached an agreement that will make Resuscitation its official journal. The editor in chief is Dr John McCabe of Syracuse, New York State. The European editor will be your President.

There is more news of the British Cardiac Society. Council recently discussed their concern at the career problems faced by many of those still in training posts. Some have had difficulty in obtaining sound advice from within their own hospitals or had good reasons for wishing to seek other counsels. Others who have been well advised still need more support or broader perspectives. We have therefore instituted a new post which is yet to have a final title. It may be Postgraduate Advisor. In any event, the need to appoint a senior and widely respected figure led to Howard Swanton who has agreed to serve in this capacity. Anyone wishing to obtain his advice can contact him through the society. On a different note, Anthony Nathan has taken over from Ronald Gold as representative of the Society on a British Standards Committee HCC92, which is the pacemaker technical committee of the Health Care Standards Policy Committee.

The authors of this newsletter have thrown caution to the winds and used both first names and surnames throughout. Those members of the society who have taken the trouble to comment on the shift towards the change in policy have indicated approval, so that we have abandoned the careful compromises of earlier months. But now a new note of controversy has been raised by David Hackett. He has asked why the society abstracts have the authors' surnames preceded by initials for men and by first names for women. He regards this as a sexist practice that is outmoded in the egalitarian times of the 1990s. Some of us like it, but we concede (some of us) that we ourselves may be anachronisms, and that in this respect we hold no strong egalitarian views. What do other members think?

Do you believe that we should be increasing the attention we pay to coronary prevention (or risk reduction)? Many cardiologists remain sceptical, not of the concept but only of the possibility for effective action. We believe this position has had some validity but should now be changing. The British Heart Foundation is active in coronary prevention and has arranged an important symposium for clinicians at the Royal College of Physicians of Edinburgh on 30 and 31 May. The programme has many hot topics such as the importance of fibrinogen and clotting factors, lipoprotein (a), and insulin resistance The course fee is £100 reduced to £50 for medical staff in training. Information can be obtained from John McGhee, Edinburgh Co-ordinates, 30 Caiystane Crescent, Edinburgh EH10 6RX (031 445 5601). We are prepared to remind members of conferences that we believe will be important, but to do this we need prompting ourselves. We will, however, be selective with a bias towards the British Heart Foundation and our affiliated groups. Would our readers like to be reminded of dates for submitting abstracts to the principal meetings and of dates for submitting applications for major grants and fellowships? Tell us. And please note our change of address.

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NOTICES

1991

The Annual Meeting of the **British Cardiac Society** will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May. The closing date for receipt of abstracts was 10 December 1990.

An international congress on angiology entitled **Angio 91** will be held in Paris on 12 to 14 April: Scientific Organising Committee Secretariat, 3 place des Vosges, 75004 Paris, France (33 1 42746464).

XII international congress on **Hemostasis and Thrombosis** will be held in Buenos Aires on 18 to 22 November: Secretary, Sarmiento 1562-4to. F, 1042 Buenos Aires, Argentina (54 1 35 6703/2798).

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BRITISH
HEART
JOURNAL

Editorial

Alcohol catheter ablation of atrioventricular conduction

The control of arrhythmia by catheter ablation was one of the highlights of clinical electrophysiology in the 1980s. Electrical catheter ablation of normal atrioventricular conduction has become an established technique for the creation of complete heart block in patients with atrial fibrillation and flutter uncontrolled by drugs, and has all but replaced the use of surgically created heart block. This technique lacks elegance because it does not cure the arrhythmia, but replaces it with a rhythm disturbance, heart block, that can be managed effectively with a pacemaker. It follows that the relative simplicity of this technique should not lead to its indiscriminate use in large numbers of patients, as most can be managed satisfactorily with antiarrhythmic drugs or may require no treatment. Electrical ablation is not without complications, and recent modifications have sought to improve the safety and efficacy.

While it seems logical to use electrical energy to destroy electrical function, there are other methods of damaging conducting tissue. On page 143 of this issue Sneddon *et al* present their experience with the new technique of transcoronary ablation of atrioventricular conduction with alcohol. They attempted ablation in 14 patients and were able to visualise and cannulate the appropriate artery in 10 (70%). After alcohol injection, chronic complete heart block was created in six of these patients, and one further patient had persistent conduction but remains symptom free without drug treatment. The modest success rate of 43% on an intention to treat basis, the potential for serious complications, and the significant increase in cardiac enzymes lead Sneddon *et al* to conclude that this technique should probably be reserved for those in whom other ablative procedures have failed. Alcohol ablation was successful in one of the three patients in whom electrical ablation had failed.

Such results stimulate not only a critical evaluation of the new technique and its place alongside other techniques, but also an appraisal of more established methods. Certainly, the conventional method of ablation, by high energy defibrillator pulses and pacing catheters, has been shown to be reasonably effective (64% complete heart block) in a large series of patients, with low complication rates.[1] In a more recent report the success rate was 88% but the incidence of serious complications was unacceptably high, especially the in-hospital mortality of 5% related to the procedure.[2]

Research into alternative methods has brought two new techniques to the fore. Low energy capacitive discharges were very successful (79–100%) and did not have the complications of high energy ablation[3–5]; this technique is indicated when the presenting arrhythmia is atrial fibrillation or flutter. Though radiofrequency ablation has not yet proved as effective for creating chronic complete heart block (36% success in the most recent series),[2] it has proved very successful in modifying atrioventricular conduction in patients with atrioventricular nodal reentrant tachycardia (42–100%).[6–8] However, despite the obvious attractions of modifying atrioventricular conduction and thereby producing a more controlled ventricular rate in atrial fibrillation or flutter while avoiding the necessity for permanent pacing, there is no evidence that such an approach improves symptoms. Therefore, we think that in patients with atrial fibrillation and flutter creation of complete heart block with low energy ablation continues to be the procedure of choice.

Given the high success rates of conventional techniques, do we need another method for non-surgical ablation of atrioventricular conduction? The answer must be that, unless the new technique guarantees success to offset its possibly greater associated risks, it is unlikely to be useful.

The use of transcoronary alcohol injection to create complete heart block deserved attention, and Sneddon *et al* have carefully assessed its benefits and risks. Although in its present form it is disappointing, other than as an alternative when other techniques have failed, the principles of the technique deserve further research. The ability to create transient complete heart block in each case with cold saline shows that the conduction system can be reached through the coronary arteries. Could toxic substances with a highly specific affinity for conducting tissue be developed? Improvement in catheter and radiological techniques holds promise that yet smaller vessels can be cannulated, with resulting greater selectivity for target organ damage. At present, conventional methods are likely to be successful in most patients and those remaining are unlikely to benefit significantly from alcohol ablation.

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ST CYRES LECTURE

Endothelium in control

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Clinical science has evolved since the days of Sir Thomas Lewis, who gave the St Cyres lecture in 1931 and whose eponymous chair I occupy. It involves still the penetration of astute clinical observation, but has come increasingly to embrace the elucidation of underlying mechanisms in the more controlled conditions of the laboratory. Its compass is being stretched by the reductionism of molecular and cell biology, but these exciting developments do not exonerate us from the ever daunting task of seeking to understand the coordinated behaviour of the whole. Perhaps biomathematics will give new impetus to our efforts to discern form in the noise. Never was there greater need for cross-talk between the different scientific disciplines and between scientists and clinicians.

The greatest growth area in cardiovascular science over recent years must surely be in the role of endothelium. Not only is there a lot of it—equivalent in mass to five normal hearts and in area to half a dozen tennis courts per standard 70 kg man—but it is coming to be recognised as a cardiovascular endocrine organ in its own right, occupying a critically strategic interface between blood and body, and subserving a multitude of regulatory roles. These range from acting as a selective permeability barrier, through vasomotor control, pro- and antithrombotic mechanisms and regulation of vascular growth, to metabolic and immunological activity. We here consider just one—namely the production of endothelium derived relaxing factor (EDRF), a powerful vasodilator substance released from the endothelium of all blood vessels of all species studied.

Endothelium derived relaxing factor

THE PHENOMENON DISCOVERED

Before 1980, the existence of EDRF was unknown. It was in 1980 that Furchgott and Zawadski published their now classic paper describing endothelium dependent vasodilatation to acetylcholine.[1] They had elucidated the paradox, long known to pharmacologists, that acetylcholine was vasodilator in vivo yet vasoconstrictor when studied in vitro with arterial strip preparations (where it transpired that the delicate endothelium is generally inadvertently removed during preparation). This explained the findings of our own studies at that time, for we had serendipitously (and initially unknowingly) encountered the phenomenon while developing an isolated perfused coronary artery preparation of the rabbit to study vasomotor regulatory mechanisms. As we gained experience with the preparation, frustratingly we met with increasing difficulty in getting the arteries to constrict.[2] Indeed constrictor responses to the usual vasoconstrictor agents were virtually abolished with better preparation due, it became apparent, to endothelial preservation.

Furchgott had suggested that the endothelium dependent vasodilator influence might be a humoral factor.[1] We developed a cascade bioassay system in which effluent from a perfused endothelialised "donor" artery perfused a denuded, pre-constricted "recipient" artery,[3] and were able to confirm that the phenomenon was indeed due to endothelial production of a humoral agent, EDRF, both tonically in the basal state and to a greater extent when stimulated, for example, by acetylcholine. By experiments in which we altered the transit time between donor and recipient vessels, we showed that EDRF is unstable, with a half life measured in seconds,[3] though it is likely to be less than a second in vivo.[4]

EDRF: THE ENDOGENOUS NITROVASODILATOR

The possibility that EDRF might be nitric oxide emerged.[5–7] Direct evidence for this was provided by Palmer and colleagues in 1987.[8] There has, however, remained a suspicion that EDRF may be not nitric oxide itself but a closely related molecule.[9] EDRF is thus the endogenous counterpart of the nitrovasodilator drugs.[10] The metabolic step involved in the production of EDRF is that of activating nitric oxide synthase to provide nitric oxide from its precursor substrate, L-arginine,[11] the supply of which seems not normally to be rate-limiting because it can be regenerated endogenously from other amino acids. The short half life of EDRF is thus explained, for nitric oxide is rapidly converted to nitrite and nitrate in the presence of water and oxygen, and even more rapidly by superoxide radicals, which are widely present in biological systems.[12 13]

ERDF RELEASE

The list of conditions now known to stimulate EDRF release is large (for reviews, see[14–17]). It includes agents liberated during platelet aggregation and thrombosis (serotonin, ATP and ADP, thrombin) (thereby implying a further mechanism whereby healthy endothelium inhibits thrombosis) and a large number of hormones and neurotransmitter substances (for example, substance P, calcitonin gene related peptide, acetylcholine, noradrenaline, vasopressin, vasoactive intestinal peptide, bradykinin, histamine) (implying means whereby (*a*) intravascular agents may transduce their signals across the endothelial barrier and (*b*) agents liberated from adventitial autonomic nerve endings on smaller arteries may exert their action after diffusion through to the endothelium). As an experimental tool, calcium ionophore can be used to stimulate EDRF release independently of receptors. Perhaps the most important physiological stimulant of EDRF release, though, is flow rate[18] acting through the relatively small longitudinal shear force experienced uniquely by the endothelium—as confirmed by experiments with fluids of different viscosity[19] and as increased with pulsatile flow.[20]

The mechanism of agonist stimulated release of EDRF from endothelial cells involves occupation of specific receptors, leading to activation of the phosphoinositol pathway and an increase in cytosolic calcium,[21–28] both from release of internally stored calcium (which causes a transient high calcium level) and from continuing influx of extracellular calcium (which maintains a level of calcium sufficient to stimulate EDRF production but which is lower that that which would stimulate prostacyclin production).[29] Shear force is thought to act through altering potassium conductance, leading by ionic interchange to an increase in cytosolic calcium.[30–32] Calcium (via calcium calmodulin) activates nitric oxide synthase[33] to produce EDRF. The stimulated production of EDRF is dependent also on the provision of mitochondrial ATP.[34] Some negative feedback control exists in that EDRF activates soluble guanylate cyclase in endothelial as in other cells (see below) and thus inhibits its own production in response to some agonists.[35 36]

ACTION OF EDRF

Nitric oxide interacts with the haem moiety present in the cytosolic enzyme, soluble guanylate cyclase, to activate it and thereby raise intracellular concentrations of cyclic GMP.[10 37–40]

An increased intracellular concentration of cyclic GMP inhibits the agonist induced activation of the phosphoinositol pathway, which is responsible for stimulating calcium influx and intracellular calcium release and thus for increasing cytosolic free calcium.[41–44] An increase in cyclic GMP in vascular smooth muscle cells therefore relaxes vascular smooth muscle tone, particularly where this is increased by receptor mediated stimulation.[45] It has analogous effects in other cell types—for example, platelets, myocardium (see below).

Haemoglobin also contains a haem moiety with which nitric oxide competitively interacts.[46 47] The sink of haemoglobulin within erythrocytes,[48] as well as haemoglobin complexed to haptoglobin in plasma,[49] ensure that EDRF has no downstream activity within the vascular compartment, as experimentally confirmed.[50] Its action is thus localised to the immediately subjacent vascular smooth muscle. Each millimetre of endothelium controls its own little bit of the vascular system.

VESSEL DIFFERENCES

EDRF activity has been demonstrated in every vessel studied—arteries, microvessels, and veins—and in every species studied,[14 16 17] with the implication that it is of primitive evolutionary origin. There are however considerable differences in the level of activity in different vessels.[2 51–54] Differential bioassay has confirmed that these are due to differences both in the response to EDRF and in its release.[55] These may be differences in basal release, flow related release, or release resulting from receptor stimulation, also with differences in specific receptor responsiveness. Differences in observed responses must also take account of differential baselines, as set by the levels of basal or flow related EDRF activity, because a "response" represents the difference between the starting level (baseline) and the end point (ceiling) of the response and will be as much influenced by the basal as by the stimulated level.[2 56] Furthermore, many of the known stimulants of EDRF act not only on endothelial receptors but also on vascular smooth muscle receptors (not always of the same subtype). The resultant response to such a "double agent" will thus depend on the relative strengths of the EDRF mediated dilator response and the direct constrictor response. Clearly there is rich potential for variation in different blood vessels, and under different physiological conditions let alone pathological ones.

It has generally been considered that veins show lower EDRF activity than arteries.[51 57] Bioassay experiments have suggested that, at least in some cases, the difference may lie more in the response to EDRF than in its release.[58] At first sight, this runs counter to the generally held clinical view that the major site of action of its pharmacological analogue, the nitrovasodilator drugs, is on the venous system.[59] This nitrovasodilator selectivity, however, probably reflects the need for most organic nitrovasodilator drugs, such as glyceryl trinitrate or the isosorbide nitrates, to undergo metabolic conversion to provide the active principle, nitric oxide, and veins seem better endowed with this metabolic pathway than arteries (while platelets seem to lack it entirely)[60 61]—these considerations do not apply to molsidomine, SIN-1, or sodium nitroprusside which are sources of nitric oxide that do not depend on this metabolic step. Comparison of EDRF activity between different blood vessels is in practice difficult because the question is not as simple as it appears. Bioassay experiments have indeed confirmed the ability of veins (for example, human saphenous vein) to relax in response to EDRF[62] and of human saphenous vein to produce EDRF.[58] However, EDRF activity depends not only on EDRF production and the response to EDRF, but also on the specific agonists used to cause constriction and to stimulate EDRF release. Much of the apparent controversy in published reports is attributable to limitations inherent in the techniques used and to vessel specific differences between endothelial responsiveness to different agonists.

Microvessels

EDRF IN VIVO

Tonic microvascular EDRF activity has been demonstrated by infusing or feeding analogues of arginine which block nitric oxide production. In the intact rabbit, for example, this causes a substantial, prolonged but reversible increase in blood pressure—interestingly without calamitous platelet aggregation.[63] Inhibition of coronary EDRF activity limits perfusion of isolated buffer perfused hearts to the point of inducing global ischaemia.[64] In the human forearm, intra-arterial infusion of an arginine analogue likewise reduces flow, illustrating the contribution of tonic microvascular EDRF activity to the human circulation.[65]

EDRF AND FLOW IN VASCULAR NETWORKS

The influence of EDRF activity on the coordinated behaviour of an intact microvascular bed has been investigated in the perfused rabbit ear, using microradiographic techniques to image simultaneously different generations of microvessels (down to about 100 μm diameter) and observe their calibre in response to changes in flow in the presence and absence of EDRF activity.[66–69] These studies illustrate the interdependence of different vessels within the bed and emphasise the need to consider the integrated behaviour of the whole vascular bed. For example, a pharmacologically induced increase in distal resistance can raise intravascular pressure and lead paradoxically to proximal dilatation, while a reduction of resistance in one part of a bed can lead to EDRF mediated dilatation as a result of increased flow throughout the bed.

Flow related EDRF activity amplifies a locally induced change in resistance in the bed, thus contributing, for example, to a metabolically mediated hyperaemic response. It also coordinates the changes in calibre throughout the bed. Furthermore, it reduces the increase in pressure needed to drive increased flow: specifically, flow (Q) was shown to be related to diameter (D) to the fourth power ($Q = aD^4 + b$, where a and b are constants) when EDRF was present but not in its absence, implying that EDRF results in progressively reduced increments of pressure in order to increase flow at high flow rates. Moreover, EDRF activity was necessary to preserve constancy of flow distribution at different flow rates: in the absence of EDRF activity, flow distribution became heterogeneous—a form of "steal".

BRANCHING GEOMETRY OF VASCULAR BEDS

Analyses of vessel diameters in relation to flow in the rabbit ear preparation have shown that the pattern of branching angles in the bed provides for optimal minimisation of power losses—an optimality of design which is lost in the absence of EDRF activity.[70]

AUTOREGULATION

The "myogenic response", which is intrinsic to vascular smooth muscle in most beds, describes the constriction induced directly by an increase in intraluminal pressure. This is a positive feedback mechanism which makes for a potentially unstable situation unless balanced by an opposing positive feedback mechanism. EDRF may be seen as answering this need, for pressure is normally coupled to flow and increased flow leads to EDRF mediated vasodilatation, thus providing a positive feedback mechanism in the opposite direction.

The myogenic response is predominantly responsible for autoregulation of flow, whereby the flow is maintained relatively constant despite changing pressure within limits. EDRF opposes this phenomenon. The relative strength of these two mechanisms determines the degree of autoregulation, as appropriate to the biological needs of different beds.[71]

PHYSIOLOGICAL IMPLICATIONS

EDRF activity is high in the microvessels. In the intact network of the rabbit ear, it was particularly high in those vessels best placed to control distribution of flow (about 100–200 μm diameter) where calculated shear force was also highest. EDRF seems to have an important physiological role in maintaining "efficiency" of perfusion. Even minor impairment of EDRF activity would have adverse effects on the efficiency and work of perfusion.

Platelets

EDRF also increases cyclic GMP concentration in platelets.[72–75] This inhibits both platelet adhesion and platelet aggregation,[76] whereas agents that increase cyclic AMP (prostacyclin, adenosine) inhibit only aggregation. It is during adhesion that platelet derived growth factor (PDGF) is released. Cyclic GMP and cyclic AMP act at different sites within the cell and their effect on aggregation is synergistic.[76]

Activated platelets release agents (for example, serotonin, adenosine diphosphate (ADP)) which stimulate intact endothelium to release EDRF; EDRF inhibits further platelet aggregation and causes local vasodilatation—a negative feedback. In the absence of endothelium, the direct action of these same agents causes further aggregation and local vasoconstriction—a positive feedback. Aggregation and constriction will thus be localised to the site of endothelial damage.

Platelets seem to have nitric oxide synthase themselves.[77] Platelet activation is associated with nitric oxide production, and nitric oxide will activate soluble guanylate cyclase in the platelets to provide some negative feedback to the activation process.[77]

Endocardium

Endothelium also lines the much trabeculated cavity of the cardiac chambers. It has recently been shown that just as vascular endothelium influences vascular smooth muscle tone so endocardial endothelium can influence contraction of underlying cardiac muscle.[78-82] Selective removal of endocardium from isolated papillary muscle preparations results in a "negative inotropic" effect which is unusual in that the duration of contraction is abbreviated but contractile behaviour early during the course of a contraction is unaltered. Effluent from cultured endocardial cells reverses this effect, thereby confirming that endocardium tonically releases a myocardial contraction prolonging factor ("endocardin"?)[80-82] of as yet unknown identity. It does not seem to be any of the obvious candidates such as an endothelin or a prostaglandin. Preliminary experiments suggest that the tonic contraction-prolonging effect of endocardium which has been shown in isolated preparations is manifest also in the intact ventricle despite the small mass of endocardium relative to myocardium.[83] Clearly, this could be important in modulating diastolic filling. Conversely, endocardium can also be stimulated to release EDRF which increases cyclic GMP concentrations[81 82 84 85] in myocardium and, like other interventions which raise myocardial cyclic GMP, shortens the duration of contraction—an effect which is indistinguishable from that of *removing* endocardium (which does not itself alter cyclic GMP concentrations).

Other sources of nitric oxide

It is becoming evident that nitric oxide is an intercellular signal which fulfils a very wide variety of physiological roles. Many cell types other than endothelium also produce nitric oxide—platelets (see above), brain,[86 87] adrenal cells,[88] non-adrenergic non-cholinergic nerve fibres,[89 90] neutrophils, monocytes,[91] and mast cells[92]; while macrophages also produce nitric oxide as part of their immunological response but probably by a different mechanism.[93 94]

Pathophysiology

There is a growing list of conditions in which EDRF activity seems to be impaired—including subarachnoid haemorrhage,[95-98] endothelial damage and repair,[99-102] ischaemia and reperfusion, atheroma, hypertension, diabetes, heart failure, lack of oestrogens,[103] and aging.[104 105] Conversely, increased EDRF production during endotoxin shock may be responsible for hypotension[106] but also perhaps for survival. Endothelium, indeed, seems to be a prime target for "cardiovascular risk factors".

SUBARACHNOID HAEMORRHAGE

Subarachnoid haemorrhage is known to be complicated by cerebral vasoconstriction. Given that haemoglobin interacts with EDRF where it can get at it, an obvious potential mechanism is suggested. Several studies now provide convincing evidence that the constriction is indeed attributable to inhibition of EDRF activity by haemoglobin.[95-98] Experimental in vivo injection of haemoglobin or whole blood into the subarachnoid space causes constriction of the intrathecal cerebral arteries associated with a reduction in their cyclic GMP content (T M Griffith, unpublished observations). The effects persist for up to a week, with histological evidence of haemoglobin in the intimal layers. This probably reflects seepage through these intrathecal arteries, which are peculiar in that they have no vasa vasorum and may be more porous than other arteries.

ENDOTHELIAL REGENERATION

Several groups have studied the effects of balloon denudation of coronary arteries followed by regrowth. Endothelium regrows within about a week but interestingly this may be followed over subsequent months by progressive and selective impairment of receptor mediated EDRF responsiveness.[99-102] These studies have important implications. Endothelial cells normally live for more than 10 years. They can obviously be kicked into rapid reproductive activity, however, by the crude insult of physical damage, after which they appear morphologically different[99 102] and can exhibit altered function for up to six months.[101] The selective impairment of EDRF responsiveness has been analysed further in the pig model, where the pattern of the impaired relaxation of coronary artery rings was shown to correspond to pertussis toxin sensitivity of these agonists and thus to dependence on a particular G protein that couples receptor occupation to cell signalling.[101 107] The endothelium seems to undergo an alteration of phenotypic expression, analogous to that which occurs in vascular smooth muscle where a change from normal contractile to synthetic phenotype underlies the proliferative growth intrinsic to atherogenesis and to the intimal hyperplasia seen after angioplasty and in graft stenosis.

ISCHAEMIA AND REPERFUSION

Ischaemia followed by reperfusion results in specific and probably prolonged impairment of EDRF responsiveness while endothelium independent responses remain unaltered.[108-111] EDRF activity is not impaired after ischaemia alone but becomes impaired progressively during the early minutes of reperfusion. Most studies have used rather long periods (for example, 60 min) of ischaemia,[108 109] but impaired EDRF responses in conduit coronary arteries have been demonstrated after even 15 minutes in vivo ischaemia (which also alters microvascular endothelial function as evidenced by protein leak).[112] Similar specific impairment of EDRF activity is evident in the coronary conduit and resistance vessels in the intact heart. The changes are probably secondary to mediators derived from reperfused ischaemic myocardium rather than reoxygenation of ischaemic endothelium itself, for endothelial cells in culture are remarkably resistant. Microvascular polymorph adhesion and plugging are known to occur during ischaemia and reperfusion.[113] Neutrophil activation releases superoxide radicals and impairs EDRF activity.[114 115] If adhesion is prevented by specific antibodies, this sequence of events is prevented.[116] Lymph draining ischaemic myocardium has been shown to contain agents chemotactic for polymorphs.[117] Adenosine which increases neutrophil cyclic AMP content and inhibits superoxide production,[118] can on the other hand ameliorate polymorph plugging and improve reflow.[109] Conversely, intracoronary infusion of complement components can cause transient polymorph adhesion and plugging even in the absence of ischaemia.[119] The suspicion is thus that oxygen free radicals are involved in this impairment of EDRF production and that they are derived predominantly from activated neutrophils in vivo.

Selective impairment of endothelium dependent relaxation evoked in vitro by aggregating platelets has been demonstrated for up to 12 weeks after reperfusion.[110] Another consequence of impaired microvascular EDRF activity after reperfusion might be a redistribution of perfusion at the expense of the vulnerable endocardium.[111]

ATHEROMA

A wide range of hyperlipidaemic atheroma models, ranging from the rabbit to the primate and from hereditary to dietary hyperlipidaemia, have consistently shown impairment of receptor mediated EDRF responsiveness in large (for example, coronary) arteries while endothelium independent dilator and constrictor responses are preserved.[120-127] It was at first thought that the layer of lipid deposition acted as a barrier interfering with EDRF diffusion to the underlying vascular smooth muscle, but it is now known that endothelial production of EDRF is impaired. The phenomenon is reversible though this takes as long as 18 months in the primate model[123] and the abnormalities have persisted for 10 weeks in the rabbit model.

Does an insult to the endothelium also affect the less easily studied microvessels? As might have been predicted, abnormalities have now been reported also in the microvessels, specifically in respect of EDRF responsiveness to acetylcholine, bradykinin, and the calcium ionophore in coronary microvessels (100–200 μm in diameter) whereas the endothelium independent response to adenosine and nitroprusside remained normal.[128,129] The experimental hyperlipidaemia that is responsible for inducing atheroma—with intimal hyperplasia, "foam" cells, and fibrosis—in the large arteries clearly also impairs endothelial function in the microvessels, with potentially adverse consequences for the "efficiency" and homogeneity of flow distribution (see the section on coronary artery disease, below).

Conversely, feeding with fish oil may enhance EDRF activity.[126,130-133] We may expect to hear more of dietary manipulation of the lipid content of cell membranes and their influence on properties such as endothelial responsiveness to stimulants of EDRF activity.

CORONARY ARTERY DISEASE

Early experimental studies with coronary artery preparations where intact endothelium abolished conventional vasoconstrictor responses had illustrated vividly how localised damage provided a model of non-specific localised constriction or "spasm".[2] Studies with clinical coronary artery disease have now produced an impressively consistent body of evidence showing that specific EDRF responsiveness is impaired in the large coronary arteries, as measured by angiographic calibre of these arteries in response to a number of interventions. Dose responses to the "double agent", acetylcholine, show a shift from dilatation in normal arteries towards increasing degrees of constriction in relation to graded severity of underlying atheroma, as evidenced by "irregularity" or "stenosis".[134,135] A similar shift towards constrictor responses was observed in angiographically smooth arteries in relation to the presence of overt disease in other coronary arteries,[136] or to the presence of known risk factors for atheroma,[137] or indeed to age.[105] The inference is that the EDRF mediated dilator response to acetylcholine is depressed in the presence of atheroma, of which angiographic evidence is an insensitive measure given the remodelling which preserves vessel calibre until the atheroma grows quite large. A similar shift from dilatation to constriction of upstream proximal arteries in relation to coexisting atheroma was seen in response to the increased flow through these large arteries induced by distal intracoronary injection of non-specific dilators such as papaverine or adenosine.[136,138] This shift in the response of proximal arteries was seen also with more physiological interventions such as exercise,[139] the cold pressor test,[140] or a pacing induced increase in heart rate.[141]

Interestingly, these two last interventions, which normally increase flow through the bed, decreased flow in the presence of non-critical upstream atheromatous stenosis, suggesting that there are corresponding changes in the responsiveness of resistance vessels. Recent studies by Drexler and colleagues provide further evidence of impaired microvascular EDRF responsiveness in the human coronary arterial bed: the increase in coronary flow induced by acetylcholine relative to that induced by endothelium independent dilatation with papaverine was found to be reduced in the presence of minor coronary artery disease and/or hypercholesterolaemia[142] (and H Drexler, personal communication).

HYPERTENSION, DIABETES, SYNDROME X, HEART FAILURE, CARDIOMYOPATHY, VEIN GRAFTS

EDRF activity in large arteries can also be impaired in experimental[143-145] and clinical[146] hypertension and in diabetes.[147-149] Impaired EDRF activity may also contribute to impotence in diabetes.[150] Both hypertension and diabetes are associated with "small vessel disease" and it is notable that the experimental combination of the two conditions can cause a form of "cardiomyopathy" that seems to be the result of focal necrosis of microvascular origin.[151]

The pathogenesis of microvascular angina (syndrome X) remains unknown.[152] A relative constrictor response to ergometrine has been described in some such patients,[153] and ergometrine is another "double agent" which both stimulates EDRF release and exerts a direct constrictor action on vascular smooth muscle.[154] It is legitimate to speculate on a possible role of impaired "feed-vessel" EDRF activity despite the limited therapeutic response to vasodilators in this condition ("lumped" pharmacological presentation of a drug may well achieve less effective dilatation than coordinated dilatation from flow stimulated release of an endogenous agent).[155]

EDRF activity in the systemic arteries has also now been reported to be impaired in heart failure[156] and in the coronary bed in congestive cardiomyopathy.[157] Conversely it has been reported to be increased by chronically elevated flow.[158] It is also impaired after preparation of vein grafts.[58]

Endothelium seems indeed to be vulnerable to many insults, with potentially far reaching pathophysiological implications.

A role in atherogenesis?

LIPOPROTEINS

Evidence is accumulating that low density lipoproteins (LDL) impair EDRF activity in vitro.[159–161] LDL can directly inactivate EDRF, but it seems likely that oxidised LDL mediates a more important and longer lasting effect. In one study, the same adverse effect on EDRF responsiveness could be induced by lysolecithin at concentrations similar to those found in the oxidised LDL: it was suggested that alteration of the composition of the endothelial lipid membrane may influence receptor function for stimulation of EDRF release.[162] LDL may be oxidised by, for example, endothelial cells, macrophages, or vascular smooth muscle cells in the arterial wall, there to be taken up by scavenger receptors on the macrophages where it accumulates to form foam cells and contribute to the atheroma.[163]

LOCALISATION OF ATHEROMA

The predilection of atheroma for certain sites implies haemodynamic influences in the process, the signal for which is thus likely to be mediated by the endothelium. The weight of evidence now points strongly to localisation of atheroma at sites of low shear stress.[164] In speculating on the possible role of EDRF in localising atheroma, two experimental observations may be relevant.

Transport of lipoproteins across vessel walls will depend on their intravascular concentration, driving pressure, wall thickness, and wall "permeability". As an example of this last determinant, Caro and Lever showed that nitrovasodilators enhanced mass transport of particles across large artery walls[165]: fewer particles accumulated on the intimal side of the media as the lattice of the medial smooth muscle was relaxed, with, by implication, faster transit across the wall. For particles, read LDL and for nitrovasodilators, read EDRF. EDRF activity is increased by high shear stress. High shear stress, via EDRF, could thus reduce the transit time of LDL across the arterial wall and the opportunity for oxidation en route. More recent work indicates that LDL moves less freely through the arterial wall than albumin, and that high transmural pressure greatly increases LDL concentrations in the intima,[166] adding further to the view that the media acts as a molecular sieve for LDL.[167] The second experimental observation derives from simple experiments in which wrapping foil around a blood vessel leads to the rapid development of atheroma.[168] One possible explanation for this is that the foil somehow prevents the egress of LDL from the adventitial surface of the vessel thereby contributing to its accumulation.

ENDOTHELIAL DAMAGE/DYSFUNCTION

Endothelial damage has long been held to be important in the atherogenic process,[169] though opponents of the hypothesis have drawn attention to the relative lack of histological evidence for endothelial damage. It is notable too that localised experimental removal of endothelium which does not damage the underlying vessel wall does not induce intimal hyperplasia.[170] Conversely, continuing minor endothelial damage as from an indwelling catheter does induce intimal hyperplasia.[171] It seems that the normal repair process after an episode of endothelial injury is self limiting, whereas prolonged stimulation of repair from recurrent endothelial damage perpetuates a chronic inflammatory response which results in the atheromatous lesion.

Endothelial cells normally divide only rarely, but they can be stimulated to divide rapidly to re-cover a denuded area. Such recently regrown cells have a somewhat different morphological appearance and their function (as manifest for example by altered EDRF responsiveness) remains abnormal for long periods. It has now been shown that other insults that fall short of causing actual denudation also result in prolonged dysfunction, associated generally with some alteration of morphological appearance. The evidence suggests that endothelium can undergo phenotypic modulation in response to several adverse stimuli, as for example the cytotoxic action of oxidised LDL. A central role of endothelium in atherogenesis might then be dependent on such phenotypic alteration, rather than on actual damage itself. Whether the altered phenotypic expression represents a single functional state characterised by both cell division and a pattern of altered function, or whether there can be variations on this theme (that is, a spectrum of altered phenotypes), remains unknown. Likewise it is not clear whether the altered state necessarily reflects the response of neighbouring endothelial cells to cryptic cell loss, or whether it can be the direct response of endothelial cells to adverse stimuli that fall short of causing actual cell death.

Reduced EDRF responsiveness is thus likely to be but one manifestation of altered endothelial function—a marker of an altered state which has other atherogenic characteristics, as for example by increasing leucocyte adhesion and attracting and promoting growth of underlying cells, leading to the atheroma which has many characteristics of a chronic local inflammatory response.

Reduced EDRF activity itself, however, could have far reaching effects which might contribute to the atherogenic process. Nitric oxide is an oxygen radical scavenger. Less nitric oxide implies more superoxide, with greater propensity to oxidise LDL as well as contribute to further cell dysfunction. Less EDRF implies less porosity of the arterial wall and longer transit time, offering greater opportunity for oxidation en route. Less EDRF implies less inhibition of platelet adhesion with its consequent very localised release of platelet derived growth factor (which may then contribute to the cascade of events underlying intimal proliferation and atheroma). Less EDRF also means lower concentrations of cyclic GMP in the artery wall, and cyclic GMP exerts antiproliferative effects in some preparations of vascular smooth muscle cells,[172-174] possibly in relation to whether they are in the contractile or synthetic phenotype.[175]

An integrated system

A lecture such as this offers a rare opportunity for indulging in an overview of the field that seeks to discern form emerging through the mists of uncertainty which always lie ahead. Technical developments that allow us to measure and analyse flow have coincided with new conceptual insights into its control. We have moved from a cardiovascular preoccupation with pressure, faute de mieux, to an era in which we are seeing an accelerating exploration of the complexities of flow. Flow after all is what the circulation is all about. It has become clear that endothelium, sited at the interface between flowing blood and the vessel wall, plays a key role in controlling vascular structure as well as tone. Future cardiovascular physicians will surely look back on the present surge in our understanding of the vascular system as a major chapter in the evolution of our specialty of cardiovascular medicine.

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ORIGINAL ARTICLES

Effect of early programmes of high and low intensity exercise on physical performance after transmural acute myocardial infarction

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Abstract

Does a programme of light exercise training after acute myocardial infarction produce the same improvement in treadmill performance as aerobic exercise training? Three hundred and eight men from a consecutive series of 479 men with transmural (Q wave) acute myocardial infarction, admitted to a single coronary care unit, were randomly allocated to eight weeks of group aerobic exercise training or group light exercise. Groups were well matched for all characteristics other than site of infarction, which did not significantly affect results. Mean (SD) physical working capacity (metabolic equivalents) determined by treadmill testing at the start of the study (in the third week after infarction) was 6·8 (2·2) *v* 6·7 (2·5) METs, at the end (in the eleventh week after infarction) 10·8 (2·3) *v* 9·9 (2·4) METs, and at 12 month review 10·8 (2·4) *v* 10·7 (1·9) METs for the exercise training group and the light exercise group respectively. The difference of 0·9 METs at the end of the study was the only significant difference between groups. There were no significant intergroup differences at any stage in resting and maximal heart rate, resting and maximal systolic blood pressure, or rate-pressure product.

Apart from a small temporarily greater physical working capacity, the physical benefits of aerobic exercise training were equally well achieved by group light exercise.

Exercise training has many claimed benefits in the rehabilitation of patients after acute myocardial infarction. Physical performance was improved significantly by such programmes.[1–3] Nevertheless, it is possible that similar physical benefits might be achieved from group programmes of similar duration that are based upon light exercise rather than high intensity exercise training. A lower level of exercise would largely remove the hazards of cardiac arrest or skeletal injury and avoid the need for medical supervision.

The Austin Hospital Cardiac Rehabilitation Trial was set up to test the hypothesis that the benefits of aerobic exercise training could be equally well achieved through a less expensive programme of light exercise based upon physiotherapy. The study was an open management trial in which male patients were randomly allocated to eight weeks in a programme of group aerobic exercise training or a programme of group light exercise. This was a consecutive series of patients admitted to a single coronary care unit. Short term and long term physical, psychological, occupational, social, and marital adjustments were investigated. The end point of this study was physical working capacity (as an estimate of maximal total body oxygen uptake) measured by treadmill testing eight weeks and 12 months after entry into the programme.

Patients and methods

Men aged less than 70 with electrocardiographic evidence of transmural acute myocardial infarction were eligible for the programme. Transmural myocardial infarction was determined according to electrocardiographic criteria of the World Health Organisation (1959), namely, new abnormal Q waves and the development of characteristic ST and T wave changes.[4] Patients with posterior myocardial infarction, as defined by Perloff,[5] were also eligible. An increase in the activity of cardiac enzymes in the serum to more than twice the upper limit of normal (normal: creatine kinase <180 IU/l, aspartate transaminase <30 IU/l) was required to confirm that the infarct was recent.

Non-transmural or non-Q wave infarction generally results in a smaller infarct,[6] a high incidence of subsequent angina,[7 8] more frequent reinfarction,[7 9 10] and more frequent coronary artery bypass graft surgery.[9 10] For these reasons, patients with non-transmural acute myocardial infarction were excluded from the study.

Short term and long term coronary prognostic indices were calculated for all patients.[11 12] The electrocardiographic infarct site was determined from the electrocardiogram.[13] For purposes of analysis, patients with anterior and lateral myocardial infarctions were grouped together, as were those with inferior and posterior myocardial infarctions. Clinical heart failure was graded by Killip class.[14] Gradings of radiographic heart failure and radiographic heart size were assessed by a portable chest radiograph.[11] A medical history of previous ischaemia and previous infarction was noted; as was electrical reversion from ventricular fibrillation.

We used the following exclusion criteria: death or cardiogenic shock in the coronary care unit; physical or psychological disability considered sufficient to impair participation in an exercise programme; residence at considerable distance from programme venues; inadequate command of English; anticipated non-compliance or expressed reluctance to participate; contamination, determined by expressed preference for one or other programme; and other reasons including early transfer to another hospital and administrative error.

At discharge from the coronary care unit, patients were randomly allocated to a programme of exercise training or light exercise rehabilitation. Hospital management of both groups of patients was identical. All patients had the same staff, advice, literature, and baseline evaluations. The randomisation procedure was based on the method of Peto *et al* by which the random allocation to treatment groups is balanced by even-numbered groups of subjects.[15] Patients were classified as having pulmonary oedema according to whether they had radiographic and/or clinical evidence of pulmonary oedema in the coronary care unit. Those with pulmonary oedema were randomly allocated as a separate group. Patients entered the trial if they had the entry exercise test and had attended one exercise class. All patients gave their informed consent to enrolment in an exercise programme and to participation in repeated exercise testing and reviews.

We analysed data by the SPSSx package. We used t tests or χ^2 tests, with Yates's correction as appropriate, to compare results in the two groups. Probability levels were rounded to three decimal places. For some comparisons of small numbers, we calculated Fisher's exact probability (one sided) to check the χ^2 value. All other probabilities quoted are two sided. The expected sample size of this trial (about 150 patients randomised to each programme) provides considerable power (95%) to detect a difference in mean physical performance as small as 1 MET in a two sided test at the 1% level of significance.

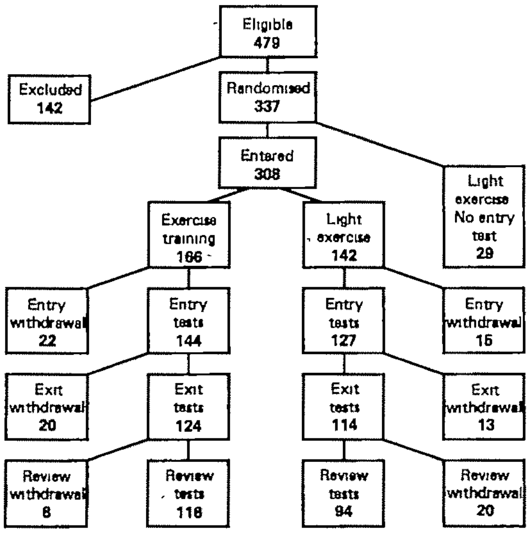
The exercise training programme complied with the recommendations of the 1979 American Heart Association Committee Report on Standards for Cardiovascular Exercise Treatment Programs.[16] Every session was attended by an exercise physiologist and physician. Resuscitation equipment was present in the gymnasium (Heidelberg YMCA). Classes were held on three days a week for eight weeks. The first attendance was usually in the second week (8–14 days) after myocardial infarction when patients watched the class. The aerobic training segment started after the first symptom limited exercise test performed in the third week (15–21 days). Exercise classes began with 10 minutes of warm up activities—generally muscle stretching on rubber mats in a gymnastics room. The aerobic segment was based on walking and jogging in the major gymnasium (a basketball court). Exercise levels were prescribed on an individual basis and calculated from the symptom limited exercise test at entry. An additional exercise test was performed in the fourth week to define modification of the training heart rate. Patients performed 30 minutes of continuous aerobic exercise at a level of energy expenditure that maintained their heart rate at 75–85% of maximum. Pulse rates were checked every five minutes. A 15 minute cooling down phase consisted of more static stretching and light calisthenics. Patients were repeatedly advised of the need to attend sessions to achieve a training effect.

The light exercise programme was conducted in a single hospital room supervised by one or two physiotherapists, with a physician available if required. Most patients first attended in the second week (8–14 days) after myocardial infarction to watch the class. From the third week, patients attended two classes a week for eight weeks. Activities included calisthenics and exercises on a stationary bicycle, a set of steps, weights, and a rowing machine. Exercise was interrupted by periods of rest, thereby reducing a significant training effect. Patients were allowed to increase their pulse rate intermittently to no greater than 20 beats per minute above the resting level. They were advised of the desirability of attending classes until they felt they need no longer attend.

Patients in both groups were also asked to walk each day at a comfortable pace for at least 30 minutes. For those patients in whom pulmonary oedema developed in the coronary care unit, entry into both programmes was postponed for two weeks.

All exercise tests were symptom limited maximal graded treadmill tests performed on a computer controlled Viagraph (IMC, Denver, Colorado, USA) exercise testing system with continuous monitoring and recording each minute of a modified 12 lead electrocardiogram. For balance, patients were allowed lightly to touch the hand rail.[17 18] Blood pressure was recorded every three minutes the conventional way by auscultation in the early stages of testing and each minute towards the end of the test, as required. Tests were stopped if disabling symptoms, hypotension (a drop in systolic blood pressure of more than 20 mm Hg compared with an earlier stage), or ventricular tachycardia (the presence of more than three successive ventricular extrasystoles) developed. Medications, including β adrenoreceptor blocking agents, were not stopped before exercise testing. Both patient groups had their entry exercise test in the third week after acute myocardial infarction. Exit tests were conducted in the eleventh week when the programmes had been completed. A review treadmill test and physical examination were conducted 12 months after trial entry.

All entry and prescription treadmill tests were performed according to fixed rate protocols.[19] The exit and 12 month tests were usually



Distribution of eligible patients showing numbers excluded, randomised, included, or withdrawn at each stage.

performed according to a Bruce protocol[17]; but under some circumstances, a fixed rate protocol was used. Physical working capacity was estimated from standard nomograms for maximal oxygen uptake and expressed as multiples of resting energy expenditure (METs) where 1 MET = total body oxygen uptake of 3·5 ml min/per kg body weight.[17] We used the rate-pressure product as an index of myocardial oxygen consumption and defined it as the highest product of simultaneously measured heart rate and systolic blood pressure during the exercise test.[20]

During the eight week rehabilitation programmes, patients received medication to control angina, blood pressure, dyspnoea, or cardiac failure, as required.

Withdrawal from the trial was defined as failure to undergo the prescribed treadmill tests. Withdrawals occurred between randomisation and entry tests (entry withdrawals), between entry and exit tests (exit withdrawals), and between exit and review tests (review withdrawals) because of death, coronary artery bypass graft surgery (undertaken only for severe angina not controlled by medication), physical disability preventing exercise testing, or when patient refusal or distance prevented attendance. Patients were encouraged to attend as many classes as possible. Non-attendance at classes, however, did not constitute withdrawal. It was recognised that incomplete attendance was likely for many reasons, including early resumption of work. Class attendances were recorded.

Table 1 Reasons for exclusion of 142 patients with acute myocardial infarction from trial

Reason	*No*
Death in CCU	37
Cardiogenic shock	6
Physical disability	33
Psychological disability	3
Distance	30
Inadequate English	11
Anticipated non-compliance	12
Contamination	5
Other	5

CCU, coronary care unit.

Table 2 Reasons for withdrawal

	Entry		*Exit*		*Review*	
Reason	*ET (n = 22)*	*LE (n = 15)*	*ET (n = 20)*	*LE (n = 13)*	*ET (n = 8)*	*LE (n = 20)*
Death	8	6	5	4	1	3
Bypass surgery	3	1	9	2	5	8
Other disability	6	3	3	2	1	3
Non-compliance	3	4	3	5	1	4
Distance	2	1	—	—	—	2

Intergroup differences were not significant (Fisher's exact test).
ET, exercise training; LE, light exercise.

Results

During the five year enrolment period, 479 men with transmural acute myocardial infarction who satisfied the trial admission criteria were admitted consecutively to the coronary care unit.

One hundred and forty two patients were excluded. The figure shows the distribution of patients excluded, randomised, and withdrawn from the trial. Table 1 shows that death and cardiogenic shock in the coronary care unit were important reasons for exclusion (43 patients) and we noted that excluded patients were older; had higher coronary prognostic indices; a higher incidence of previous infarction; and a greater incidence of clinical cardiac failure, radiographic cardiac failure, and increased radiographic heart size.

Three hundred and thirty seven patients were randomised, 166 to exercise training and 171 to light exercise. Twenty nine consecutive patients randomised to light exercise were allocated to a group that did not have an entry exercise test so that any effect of the entry exercise test could be separately examined. The admission characteristics of these 29 patients, who are not included in the current analysis, were not different from the 142 who remained in the light exercise group. Of the 308 remaining patients, 34 were classified as having pulmonary oedema in the coronary care unit.

Fifty (30%) patients in the exercise training group and 48 (34%) in the light exercise group were withdrawn from the study (table 2). Patients who were withdrawn at entry and exit were older (mean age) and had higher coronary prognostic indices, more clinical and radiographic evidence of heart failure, and previous ischaemia and previous infarction than did patients who completed their programmes. No events requiring admission to hospital occurred during treadmill tests or classes in either group.

There were 238 men (236 white) who completed their exercise programmes by attending for an exit treadmill test. One hundred patients (42%) held white collar jobs and 138 (58%) had blue collar ones. Fifty eight per cent (138) of the 238 patients were cigarette smokers up to the time of admission to hospital. There were no significant differences in these characteristics between the exercise groups. Table 3 shows the physical entry characteristics of the 238 patients. These characteristics were well matched on all criteria but one: more patients in exercise training had anterior infarction (p = 0·073). The admission characteristics of

Table 3 Admission characteristics of 238 patients who had entry and exit treadmill tests

Variable	*ET (n = 124)*	*LE (n = 114)*
Age (yr)	52 7 (8·2)	52 0 (8 9)
Weight (kg)	80·5 (10 5)	79 7 (11 5)
Height (cm)	174·0 (6·9)	174·5 (6·4)
Total cholesterol (mmol/l)	6·1 (1·4)	6·1 (1 3)
Coronary prognostic index		
Short term (Norris)	5·2 (1·8)	5 2 (1 9)
Long term (Norris)	3 4 (2 3)	3 5 (2·4)
Missing	2	
Enzyme activity*		
CK (n < 180 IU)	1790 (1067)	1958 (1139)
AST (n < 30 IU)	273 (151)	293 (183)
Infarct site (n(%))†		
Anterior/lateral	61 (49)	42 (37)
Inferior/posterior	63 (51)	72 (63)
Failure (Killip class) (n(%))		
(1) Lungs clear	74 (60)	75 (66)
(2) Basal crepitations	46 (37)	35 (31)
(3) Upper crepitations	4 (3)	4 (3)
Failure (radiographic) (n (%))		
Lungs clear	86 (71)	72 (63)
Venous congestion	27 (22)	33 (29)
Interstitial oedema	5 (4)	5 (4)
Pulmonary oedema	4 (3)	4 (4)
Missing	2	
Pulmonary oedema		
Clinical and/or radiographic evidence (n (%))	9 (7)	10 (8)
Radiographic heart size (n(%))		
Normal	86 (71)	78 (68)
Borderline	31 (25)	28 (25)
Enlarged	5 (4)	8 (7)
Missing	2	
Previous ischaemia (n(%))	28 (23)	22 (19)
Previous infarction (n(%))	10 (8)	10 (9)
Electrical reversion (n(%))	12 (10)	7 (6)

Results are expressed as mean (SD) and as number of patients (%).
*Excludes patients who underwent electrical reversion
†The intergroup difference in infarct site is not statistically significant ($p = 0\ 073$).
ET, exercise training; LE, light exercise.

the 210 patients who attended for review exercise tests at 12 months were not significantly different from those of the 238 who had entry and exit exercise tests.

Because exercise training classes were held three times a week (compared with twice a week for light exercise) and more definite encouragement was given to the patients to attend classes, patients attended exercise training more often and over a longer period. Of the exercise training patients, 65% attended more than three quarters of the total classes possible and 89% attended more than half. Only 41% of light exercise patients attended more than three quarters of their classes and 75% attended more than half ($p < 0{\cdot}001$). Over 90% of patients in each group claimed that they complied with advice to walk each day for at least 30 minutes.

Table 4 Medication at time of treadmill tests

	Entry		*Exit*		*Review*	
Treatment	*ET (n = 124)*	*LE (n = 114)*	*ET (n = 124)*	*LE (n = 114)*	*ET (n = 116)*	*LE (n = 94)*
Diuretic	30 (24)	29 (25)	28 (23)	28 (25)	28 (24)	23 (24)
Digoxin	5 (4)	5 (4)	3 (2)	5 (4)	3 (3)	7 (7)
β Blocker*	12 (10)	12 (11)	22 (18)	22 (19)	23 (20)	23 (24)
Calcium antagonist	17 (14)	18 (16)	14 (11)	22 (19)	14 (12)	14 (15)
Hypotensive	6 (5)	4 (4)	6 (5)	5 (4)	7 (6)	4 (4)
Glyceryl trinitrate	11 (9)	12 (11)	7 (6)	10 (9)	10 (9)	4 (4)
Nitrate	3 (2)	5 (4)	1 (1)	2 (2)	2 (2)	1 (1)
Antiarrhythmic	6 (5)	8 (7)	5 (4)	6 (5)	2 (2)	1 (1)
Psychotropic	10 (8)	10 (9)	11 (9)	5 (4)	13 (11)	8 (8)
Other	30 (23)	18 (16)	30 (23)	26 (23)	30 (26)	19 (20)

Results are expressed as number of patients (%).
*There was a similar and significant ($p < 0\ 014$) increase in total β blocker treatment between entry and exit in both groups (24 *v* 44). There were no significant intergroup differences in any type of medication at entry, exit, or review.
ET, exercise training; LE, light exercise.

At the time of each exercise test there were no intergroup differences for any form of medication (table 4). At each stage similar proportions of patients were taking β adrenoreceptor blocking medication. The only significant change in medication between entry and exit tests in both groups was an increase in the use of β adrenoreceptor blocking drugs (24 patients at entry test and 44 patients at exit test ($p = 0{\cdot}014$)).

The distributions of treadmill test protocols were similar in both study groups (table 5). At entry most patients had fixed rate protocols with increments of 4% in the incline from horizontal every three minutes at a speed of 3·2 km per hour or 4·8 km per hour. A few patients who showed and claimed rapid recovery and considerable fitness had their entry test at 5·6 km per hour. The Bruce protocol was mainly used at exit (83%) and 12 month review (92%), but some patients who were unfit or who had difficulty in handling a simultaneous increase of speed and incline had a fixed rate protocol test.

Table 6 sets out the treadmill test results. At entry, exit, or 12 month review tests there were no significant intergroup differences in mean resting heart rate, resting systolic blood pressure, maximal heart rate, maximal systolic blood pressure, or rate pressure product. Further, there were no significant differences between groups in the reasons for stopping treadmill tests, nor were there differences between groups at any test in the distribution of the degree of ST segment depression. While physical working capacity during the entry test was not significantly different between groups, at the exit test there was a significant mean difference of 0·9 MET between the groups ($p = 0{\cdot}002$). At the 12 month review, there was no significant intergroup difference in physical working capacity.

Between the entry and exit tests the physical working capacity (METs (SD)) increased significantly more with exercise training (4·0 (1·9)) than with light exercise (3·1 (2·0)) ($p < 0{\cdot}001$). Between the exit test and review test the physical working capacity in the 94 patients in light exercise was 0·6 (1·7) METs compared with −0·1 (1·6) METs in the 116 patients in exercise training ($p = 0{\cdot}007$).

We performed subset analyses to assess whether different distributions of the infarct site influenced the observed difference in physical working capacity between the exercise training group and light exercise group during the exit test (table 7). For both sites, the physical working capacity for the entry test was similar for patients in each programme. The exit test performances of both exercise training subsets were higher than those of the light exercise subsets with similar infarction sites. Patients who had pulmonary oedema followed the same trends as did those without (table 7).

Discussion

We compared the physical benefits of two programmes of different levels of exercise. The study was not designed to answer the question whether rehabilitation programmes based

Table 5 Treadmill test protocols

Protocol	*Entry* ET (n = 124)	*Entry* LE (n = 114)	*Exit* ET (n = 124)	*Exit* LE (n = 114)	*Review* ET (n = 116)	*Review* LE (n = 94)
Fixed rate*						
3·2 km/h (2·0 mph)	65 (53)	61 (53)	3 (2)	2 (2)	3 (3)	1 (1)
4·8 km/h (3·0 mph)	56 (45)	52 (46)	10 (8)	14 (12)	3 (3)	6 (6)
5·2 km/h (3·5 mph)	3 (2)	1 (1)	6 (5)	6 (5)	1 (1)	3 (2)
Bruce	—	—	105 (85)	92 (81)	109 (94)	84 (89)

*Fixed rate protocols with stages of three minutes and a 4% increase in incline at each stage.
Results are expressed as number of patients (%).
There were no significant differences in the distribution of treadmill protocols at any stage
ET, exercise training; LE, light exercise.

upon group exercise are more effective than usual medical care and an individual programme of exercise and walking at home.

The main finding of the study was that though physical working capacity, assessed by treadmill performance, increased more in the exercise training group than in the light exercise group, the difference was small and only temporary. The difference was not accompanied by a significant mean intergroup difference in rate-pressure product.

The results of our study are likely to apply widely. The Austin Hospital serves both as a community hospital and as a major university teaching hospital. The pattern of patient admissions to the coronary care unit, either directly or through the emergency department, is similar to that in most major hospitals in Australia and elsewhere. Exclusions were only for defined physical, psychological, or geographical reasons. Death was the commonest reason for both exclusion and withdrawal; mortality (13% by one year) was similar to that reported in other investigations.[21 22] The number of randomised patients withdrawn at each stage was small. Death (9% and coronary artery bypass graft surgery (9%) were the main reasons for these withdrawals.

The two exercise protocols tested in this trial are representative of the protocols followed elsewhere. The exercise training programme was based on the recommendations of the 1979 American Heart Association report,[16] while the light exercise programme conformed to common exercise based rehabilitation programmes offered to cardiac patients in Australian hospitals.

The end point in this study, physical working capacity, was determined by performance on a treadmill. Nomograms for maximal oxygen uptake are regarded as appropriate measures for both individual and group studies,[17 19] though some limitations have been suggested.[23] Maximal oxygen uptake correlates well with performance on a treadmill but the standard equations tend to overpredict performance.[24] Routine direct measurement of maximal oxygen uptake in large numbers of patients is impractical and the patient's performance on a treadmill (expressed in METs) is generally regarded as an appropriate measure of physical working capacity. Maximal oxygen uptake and performance on the treadmill were similar for fixed rate and Bruce exercise protocols.[23 25]

Groups were well matched except for the site of infarction. This, however, did not distort the overall results of the trial. The other possible source of bias, the withdrawal of patients for coronary bypass surgery, did not significantly affect the results either.

In the exercise training group, the mean increment in physical working capacity achieved after eight weeks was similar to the outcome of gymnasium training in the study of DeBusk *et al*, and this result was consistent with the similarities between our exercise training and their gymnasium training programmes.[3] The increment in mean physical working capacity after eight weeks in our light exercise group was greater than the spontaneous improvement during a similar period.[3 26] It was similar to the improvement reported by DeBusk *et al* by a home exercise training programme[3] but greater than that achieved by both home and group training in their subsequent study.[26] Though our light exercise programme was designed to reassure patients about the safety of activity during convalescence rather than to achieve a training effect, and though most of the patients in this group attended fewer classes than those in the exercise training group, the programme of light exercise contributed to an increase in physical working capacity. Compliance with advice and encouragement to walk and exercise daily, with twice weekly group support in this aim, was likely to have led to progressive training of those muscle groups used during the tests on the treadmill.

In a smaller study, Blumenthal *et al* found no significant increase in maximal oxygen consumption during treadmill testing between groups enrolled in exercise training pro-

Table 6 Treadmill test results (mean (SD))

Variable	*Entry* ET (n = 124)	*Entry* LE (n = 114)	*Exit* ET (n = 124)	*Exit* LE (n = 114)	*Review* ET (n = 116)	*Review* LE (n = 94)
HR	83·9 (14·2)	84·3 (13·8)	81·0 (14·7)	82·3 (13·5)	78·1 (12·4)	77·1 (15·0)
SBP (mm Hg)	116·5 (18·0)	117·7 (15·2)	121·2 (16·1)	121·1 (18·0)	130·4 (18·5)	126·9 (18·3)
HR max	147·7 (19·5)	145·8 (21·4)	156·6 (20·6)	153·3 (20·7)	157·6 (22·1)	154·9 (22·9)
SBP max (mm Hg)	153·3 (25·1)	151·5 (28·8)	161·7 (27·0)	159·7 (27·8)	167·5 (26·6)	167·3 (26·7)
RPP × 10^{-2}	223·5 (52·5)	220·0 (57·5)	250·4 (57·9)	242·8 (58·8)	263·0 (61·6)	255·2 (58·8)
PWC (METs)	6·8 (2·2)	6·7 (2·5)	10·8 (2·3)*	9·9 (2·4)*	10·8 (2·4)	10·7 (1·9)

*PWC at exit test is the only significant intergroup difference p = 0·002).
ET, exercise training, LE, light exercise
HR, resting heart rate standing (beats per minute); HR max, maximal heart rate during test (beats per minute), PWC, physical working capacity, RPP, rate-pressure product, SBP, resting systolic blood pressure standing, SBP max, maximal systolic blood pressure during test.

Table 7 Physical working capacity (METs (SD)) at entry and exit tests according to infarct site and pulmonary oedema at admission

Infarct size	*ET*	*LE*	*p*
Anterior	(n = 61)	(n = 42)	
Entry	6·4 (2·1)	6 4 (2 6)	NS
Exit	10·8 (2·3)	9·5 (2 4)	0 008
Increment	4·4 (2 0)	3 1 (2 0)	0 003
Inferior	(n = 63)	(n = 72)	
Entry	7·1 (2·3)	6 9 (2 4)	NS
Exit	10·8 (2·4)	10 0 (2 4)	0 07
Increment	3·7 (1·6)	3 1 (1 9)	0·06
Pulmonary oedema	(n = 9)	(n = 10)	
Entry	5·7 (2·2)	5 0 (1 3)	NS
Exit	9 9 (2·9)	8·3 (1 9)	NS
Increment	4 2 (1·4)	3 4 (1 9)	NS

ET, exercise training; LE, light exercise.

grammes of high or low intensity.[27] Their patients were also active, walking daily, as well as attending their exercise sessions.

Our study shows that, in the first weeks after myocardial infarction, there is a significant slowing of resting heart rate and a rise in systolic blood pressure towards preinfarction values. The achievable maximal heart rate and maximal systolic blood pressure also increase. In consequence, rate-pressure product increases significantly during the initial weeks after myocardial infarction. This increase was no larger in the exercise training group than in the light exercise group.

It seems that differences in maximal oxygen uptake caused by aerobic exercise training arise largely from an effect on peripheral muscle groups used for walking, rather than from a central cardiopulmonary · effect. This conclusion is supported by other studies.[28–30] Indeed, it would be unreasonable to expect a central cardiac or respiratory training effect from an eight week programme of three sessions per week in middle aged or elderly individuals.

Mobilisation and resumption of normal activities after a period of bed rest are known to be associated with rapid recovery of functional capacity.[31] We showed that a low cost, low intensity group exercise programme was almost as effective in the short term and was as effective at one year as aerobic exercise training for the rehabilitation of patients after acute myocardial infarction.

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Lack of correlation between P pulmonale and right atrial overload in chronic obstructive airways disease

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Abstract

The correlation between P pulmonale and right atrial overload in chronic lung disease was studied. Right atrial pressure, pulmonary artery pressure, and cardiac output were measured with a Swan-Ganz catheter in nine patients with chronic lung disease and P pulmonale on the electrocardiogram (P wave amplitude of ≥ 2·5 mm (0·25 mV) in leads II, III, and aVF. The results were compared with those in six patients with an atrial septal defect (left to right shunt ≥ 50%) and six patients with pulmonary hypertension (mean pressure ≥ 30 mm Hg without left sided heart disease). Right atrial volume and wall thickness were measured in 10 cases of P pulmonale among 1000 necropsy cases and compared with 141 normal hearts from the same series.

The patients with P pulmonale did not show a significant increase in right atrial or pulmonary artery pressures. None of the patients with an atrial septal defect or pulmonary hypertension had P pulmonale on the electrocardiogram. In the necropsy cases of P pulmonale mean (1 SD) in right atrial volume (32 (12) ml) and wall thickness (1·5 (0·7) mm) were not significantly increased (40 (14) ml and 1·4 (0·5) mm in the normal hearts). There was a significant inverse relation between the presence of P pulmonale and the cardiothoracic ratio. In all the patients with P pulmonale chest *x* ray showed a low cardiothoracic ratio, a considerably depressed diaphragm, and a pendulous heart.

This study showed no correlation between P pulmonale and right atrial overload in chronic lung disease. A more vertical anatomical position of the heart, particularly of the right atrium, seems to be the major factor responsible for generation of P pulmonale in chronic airways disease.

Peaked, tall, and narrow P waves in leads II, III, and aVF in lung disease are called P pulmonale. Though many factors such as verticalisation of the heart,[1 2] increased residual volume,[3] and impaired lung function[4 5] have been reported to be correlated with these changes in the P wave, right atrial overload (right atrial enlargement or increased right atrial pressure or both) is still thought to be responsible for P pulmonale in lung disease, especially in cor pulmonale.[6]

Because the relation between haemodynamic function and P wave variables has been little studied we investigated haemodynamic function in patients with chronic obstructive airways disease and the presence of P pulmonale (≥ 2·5 mm in leads II, III, and aVF). We compared this with P wave configuration in patients with atrial septal defect and pulmonary hypertension, conditions that increase right atrial volume and pressure respectively, and we studied the correlation between the amplitude of the P waves and the right atrial overload.

Patients and methods

PATIENTS

We studied nine patients with chronic lung disease and P pulmonale between May 1987 and August 1989 at Tokyo Metropolitan Geriatric Hospital. P pulmonale was defined by the following criteria: the amplitude of the P waves in all of leads II, III, and aVF was ≥ 2·5 mm and the duration of the P wave was ≤ 0·10 s. As control groups we also studied six patients with atrial septal defect (left to right shunt ≥ 50%) and six with pulmonary hypertension (mean pressure ≥ 30 mm Hg) that was not secondary to left sided heart disease. These conditions increase right atrial volume and pressure respectively. Haemodynamic function was assessed in these two groups at the same hospital between June 1982 and June 1987. Patients with atrial fibrillation were excluded. To evaluate the relation between P pulmonale and right atrial overload we studied 10 patients who met the criteria for P pulmonale (amplitude ≥ 0·25 mV in each of lead II, III, and aVF) and 141 patients without any significant clinical findings or cardiac abnormalities at necropsy. These cases came from a consecutive series of 1000 necropsies.

METHODS

In every patient we measured the right atrial and pulmonary artery pressure and cardiac output with a Swan-Ganz catheter and the amplitude and axis of the P waves in the frontal plane to evaluate P wave changes caused by right atrial volume load or pressure load or both. We examined chest radiographs to correlate the cardiothoracic ratio and the shape of the heart with the P wave variables. In each group we studied the correlation between the amplitude and axis of the P waves in the frontal plane and indices of haemodynamic function and the cardiothoracic ratio. In the necropsy cases we measured the thickness of the right atrial and ventricular walls and the volume of the right atrium. We used slide calipers to measure the thickness of the right atrial wall at the site of the pectinate muscle and the compact zone of the right ventricular wall 1 cm below the pulmonary valve. We calculated the right atrial volume by the following formula, assuming that the right atrium was spherical, as previously reported.[7]

$$\text{RA volume} = \frac{4\pi}{3}\left(\frac{\phi\text{RA} + \frac{T}{\pi}}{2\pi}\right)^3$$

when ϕRA is the length of the circle of longitude above the tricuspid valve; π is Pi; and T is the circumference of the tricuspid valve ring. We used the t test to analyse data. A p value of $< 0{\cdot}05$ was regarded as significant.

Results

P PULMONALE (TABLE 1)

Two patients had chronic obstructive airways disease and seven had old pulmonary tuberculosis. The mean (1 SD) amplitude and axis of the P waves in the frontal plane were 2·79 (0·25) mm (range 2·50–3·20 mm) and +81 (6)° (range +70 to +90°) respectively. The mean right atrial pressure was normal (2 (2) mm Hg). In the pulmonary artery the systolic pressure was 30 (5) mm Hg and the mean pressure was 17 (4) mm Hg. None of the patients had significant pulmonary hypertension. The cardiac index was normal in all but one patient. Chest radiographs showed a low cardiothoracic ratio (46 (7) %) (range 35–55%) in all and even the seven patients with old tuberculosis showed compensatory hyperinflation as well as the constricting changes of the lung caused by tuberculosis. As a result, there was considerable depression of the diaphragm in all. Lung function tests were as follows: vital capacity: 51 (12) % (range 30–63%), forced expiratory volume in 1s 75 (15) % (range 51–93%), and oxygen, 71 (18) mm Hg (range from 40–93 mm Hg) and carbon dioxide 45 (8) mm Hg (range 32–56 mm Hg) tension in arterial blood.

ATRIAL SEPTAL DEFECT (TABLE 2)

The chest radiographs and echocardiograms showed considerable dilatation of both the right atrium and ventricle. Mean pulmonary arterial pressure was 26 (9) mm Hg and mean right atrial pressure 4 (3) mm Hg. The mean amplitude of the P waves in leads II, III, and aVF was 0·96 (0·54) mm (range 0·10–1·70 mm) and no patient had P pulmonale. The axis of the P waves in the frontal plane was +65 (26)° (range +15° to +90°). In this group the chest radiographs showed considerable cardiomegaly (cardiothoracic ratio 68 (3) %).

PULMONARY HYPERTENSION (TABLE 3)

Mean pulmonary arterial and right atrial pressure were significantly higher (53 (25) mm Hg and 8 (5) mm Hg respectively) than in patients with P pulmonale. None the less, the mean amplitude of the P waves in leads II, III, and aVF was 0·93 (0·42) mm, and even the maximal amplitude was only 2·0 mm. No patients in this group had P pulmonale. The axis of the P wave in the frontal plane was + 59 (21)°. The cardiac index was low in four patients and normal in

Table 1 Clinical characteristics of the patients with P pulmonale

				Amplitude of P waves in II, III, aVF (mm)				*Haemodynamic function*			
Case	*Age (yr)*	*Sex*	*Underlying disease*	*Average*	*Maximum*	*Minimum*	*P axis*	*PAP (m)*	*mRAP*	*CI*	*CTR (%)*
1	77	M	COAD	2·93	3·0	2·8	+90	22/6 (11)	0	2·26	42
2	72	M	COAD	2·66	2·8	2·5	+80	26/8 (14)	6	3·28	51
3	72	M	Old TB	2·50	2·5	2·5	+85	28/8 (15)	0	2·07	37
4	69	F	Old TB	2·60	2·8	2·5	+85	28/10 (16)	2	3·81	53
5	72	M	Old TB	2·70	2·8	2·5	+85	32/12 (19)	1	2·80	52
6	81	F	Old TB	3·00	3·5	2·5	+75	38/14 (22)	1	3·30	48
7	59	M	Old TB	3·20	3·7	2·6	+70	38/18 (24)	5	3·41	41
8	59	F	Old TB	2·53	2·8	2·5	+75	28/8 (15)	1	2·27	55
9	69	M	Old TB	3·00	3·2	2·8	+80	34/12 (19)	3	2·30	35

CI, cardiac index (l/mm/m²); COAD, chronic obstructive airways disease; CTR, cardiothoracic ratio; mRAP, mean right atrial pressure (mm Hg); TB, pulmonary tuberculosis; PAP (m), pulmonary artery pressure (mean) (mm Hg)

Table 2 Clinical characteristics of patients with an atrial septal defect

			Amplitude of P waves in II, III, aVF (mm)				*Haemodynamic function*			
Case	*Age (yr)*	*Sex*	*Average*	*Maximum*	*Minimum*	*P axis*	*PAP (m)*	*mRAP*	*L→R shunt (%)*	*CTR (%)*
1	71	F	0·67	1·0	0·3	+75	46/18 (27)	4	68	63
2	56	F	0·97	1·1	0·7	+90	42/18 (26)	2	74	67
3	62	F	1·03	1·3	0·5	+60	29/7 (14)	0	50	71
4	71	F	0·10	0·1	0·1	+15	67/23 (38)	5	68	72
5	70	F	1·27	1·5	1·0	+75	35/10 (18)	4	60	66
6	78	M	1·70	1·9	1·4	+75	40/15 (33)	8	71	69

L→R, left to right. See footnote to table 1 for other abbreviations.

Table 3 Clinical characteristics of patients with pulmonary hypertension

				Amplitude of P waves in II, III, aVF (mm)				Haemodynamic function			
Case	Age (yr)	Sex	Underlying disease	Average	Maximum	Minimum	P axis	PAP (m)	mRAP	CI	CTR (%)
1	79	F	PTE	0·73	0·8	0·6	+75	88/20 (43)	6	1·48	67
2	87	M	COAD	1·43	1·5	1·3	+90	54/24 (34)	3	2·40	43
3	77	F	PTE	0·67	0·9	0·3	+60	52/31 (38)	15	2·20	71
4	52	M	PTE	0·60	1·0	0·3	+30	148/67 (94)	14	1·50	58
5	73	M	PTE	1·50	2·0	0·8	+55	110/55 (73)	4	2·72	53
6	81	F	PTE	0·63	1·0	0·4	+45	70/15 (35)	5	1·86	59

PTE, pulmonary thromboembolism. See footnote to table 1 for other abbreviations.

Table 4 Clinical characteristics and findings at necropsy in 10 patients with P pulmonale

				Mean amplitude of P waves (II, III, aVF) (mm)	Right atrium		Right ventricle	
Case	Age (yr)	Sex	Underlying disease		Volume (ml)	Thickness	Thickness (mm)	CTR (%)
1	82	M	COAD	2·83	36	1·1	2·5	44
2	79	F	COAD	2·80	15	1·0	2·2	52
3	88	M	COAD	3·17	36	3·0	3·0	45
4	65	M	COAD	2·57	23	1·2	4·0	39
5	78	F	COAD	2·50	43	2·3	5·8	46
6	73	M	COAD	2·67	22	1·2	4·0	36
7	71	M	COAD	3·33	33	1·0	2·5	43
8	84	M	Old TB	2·93	43	1·0	4·0	46
9	74	M	Old TB	2·77	51	1·6	1·8	49
10	85	F	None	2·87	21	1·2	3·0	44
Mean 1 SD				2·84 (0·25)	32 (12)	1·5 (0)	3·3 (1·2)	44 (5)*
Necropsy cases with normal heart				(n=141)	40 (14)	1·4 (0·5)	3·8 (1·2)	53 (7)*

*P < 0·01. See footnote to table 1 for abbreviations.

Table 5 Clinical (mean (1 SD)) characteristics of each group

	P pulmonale (group 1) (n=9)	ASD (group 2) (n=6)	PH (group 3) (n=6)	p Value		
				1 v 2	1 v 3	2 v 3
Age (yr)	70·0 (7·3)	68·0 (7·8)	74·8 (12·1)	NS	NS	NS
Sex (F/M)	3/6	5/1	3/3			
P waves						
Mean amplitude*	2·79 (0·25)	0·96 (0·54)	0·93 (0·42)	0·01	0·01	NS
Axis (°)	+81 (6)	+65 (26)	+59 (21)	NS	0·05	NS
Pressure data (mm Hg)						
mPAP	17 (2)	26 (9)	53 (25)	NS	0·05	0·05
mRAP	2 (2)	4 (3)	8 (5)	NS	0·05	NS
CI (l/min/m^2)	2·83 (0·63)		2·03 (0·50)		0·05	
CTR (%)	46 (7)	68 (3)	59 (10)	0·01	0·05	NS

*Mean amplitude in leads II, III, and aVF (mm).
ASD, atrial septal defect; PH, pulmonary hypertension. See footnote to table 1 for other abbreviations.

two. The chest radiographs showed moderate cardiomegaly (cardiothoracic ratio 59 (10)%).

NECROPSY FINDINGS IN 10 PATIENTS WITH P PULMONALE (TABLE 4)

The average amplitude of the P waves in leads II, III, and aVF was 2·84 (0·25) mm in patients with P pulmonale and 0·63 (0·41) mm in 141 patients with normal hearts ($p < 0·01$). Right atrial volume and wall thickness were similar in patients with P pulmonale and in controls (32 (12) ml *v* 44 (5) ml; 1·5 (0·7) mm *v* 1·4 (0·5) mm respectively) as was the thickness of the right ventricle (3·3 (1·2) *v* 3·8 (1·2) mm). The chest radiographs of all patients with P pulmonale showed that the cardiothoracic ratio (44 (5) %) was significantly smaller than in the controls (53 (7) %, $p < 0·01$) and that the heart was pendulous.

Table 5 shows the data for each of the groups.

Discussion

Peaked, tall, and narrow P waves in leads II, III, and aVF are accepted criteria for P pulmonale, but these features have no quantitative definition. Controversy about the implication of P pulmonale may derive from its ambiguous definition. We selected patients with chronic airways disease who had very tall P waves (≥ 2·5 mm) in each of leads II, III, and aVF. In this group with P pulmonale, none of the

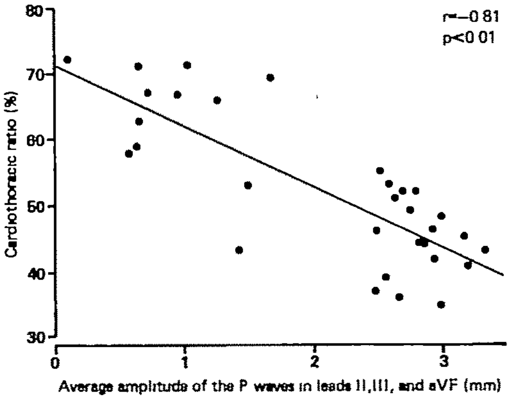

Figure 1 Relation between the mean amplitude of the P waves in leads II, III, and aVF and the cardiothoracic ratio.

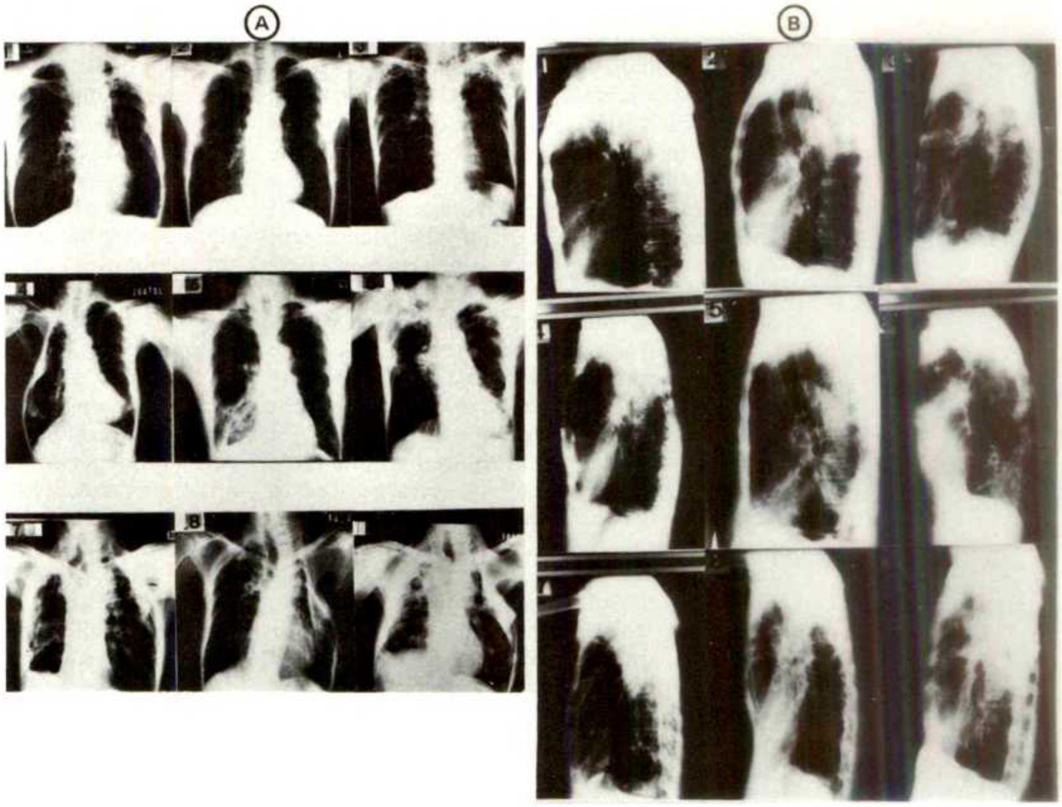

Figure 2 Chest radiographs in patients with P pulmonale. Posteroanterior views (A) and lateral views (B) showing straightened right and posterior cardiac borders respectively. There was no significant enlargement of the right atrium. Both views also show appreciable depression of the diaphragm.

patients showed significant increase in the right atrial or pulmonary artery pressure, and in eight of the nine patients cardiac output was normal. In contrast, none of the patients with atrial septal defects (which load the right atrium and right ventricle with increased volume) or with pulmonary hypertension (which loads the right atrium and ventricle with increased pressure) had P pulmonale. At necropsy 10 patients with P pulmonale showed no evidence of right atrial overload compared with the normal hearts; though in two patients there was hypertrophy of the pectinate muscle of the right atrium. Caird and Wilcken also found little correlation between P pulmonale and anatomical abnormality of the right atrium.[3] Saha reported that right atrial enlargement or increased right atrial pressure on both are important factors for the change of the P waves in cor pulmonale, in addition to the combination of tachycardia, increased residual volume, and increased intrathoracic pressure.[6] There were no patients with P pulmonale in our group of patients with pulmonary hypertension—the disease most likely to cause cor pulmonale. None of the patients with atrial septal defect showed P pulmonale, despite the right atrial enlargement caused by volume overload. So we found no correlation between P pulmonale and right atrial enlargement or increased right atrial pressure.

Spodick *et al* found that the shift of the P axis to the right as well as increased P wave amplitude was associated with appreciable impaired lung function.[4] All our patients with P pulmonale also showed impaired lung function. Almost all of them, however, showed normal haemodynamic function. Our data showed that impaired lung function did not always correlate with right atrial overload, and

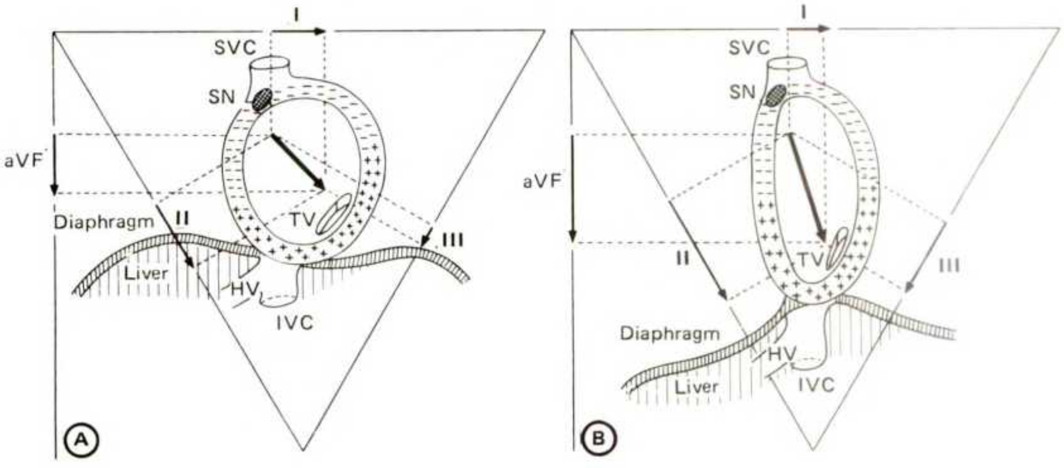

Figure 3 Relation between the right atrium and the diaphragm showing the direction of the P vector in the frontal plane and the amplitude of the P waves reflected to the leads in the frontal plane (I, II, III, aVF) when the P vector showed maximum intensity. (A) Normal relation. (B) When the diaphragm is depressed. SVC, superior vena cava; IVC, inferior vena cava; SN, sinus node; HV, hepatic vein; TV, tricuspid valve; −, heart muscle depolarised; +, heart muscle at resting membrane potential.

right atrial overload did not correlate with P pulmonale, either.

P pulmonale correlated negatively with the cardiothoracic ratio ($r = -0{\cdot}81$, $p < 0{\cdot}01$) (fig 1). The cardiothoracic ratio in the group with P pulmonale was significantly lower than in the groups with atrial septal defect or pulmonary hypertension and chest radiographs showed considerable depression of the diaphragm caused by primary or compensatory hyperinflation of the lungs. The chest radiographs showed that the right cardiac border was straightened and deviated to the left side in the posteroanterior view. This finding indicated the absence of significant enlargement of the right atrium compared with those of patients with atrial septal defect, who showed considerable cardiomegaly caused by the enlargement of both the right atrium and ventricle. Lateral views also showed a straightened posterior cardiac border (fig 2).

The position of the heart is determined by its attachment to the mediastinum by the great vessels of the ascending aorta, pulmonary artery and vein, and superior vena cava in the upper portion and by the pericardium in the posterior portion. The lower part of the heart, however, is fixed by only the inferior vena cava. Because the diaphragm was depressed the inferior vena cava was displaced inferiorly and the right atrium was stretched between the superior and inferior venae cavae and was extended vertically (fig 3). In the atrium an impulse formed in the sinus node spreads radically along the wall unlike in the ventricle where it is conducted from the endocardium toward the epicardium. The direction of the maximum P wave vector in sinus rhythm is then usually down towards the left and anteriorly or posteriorly. Because the right atrium was stretched and extended between the superior and inferior venae cavae, the direction of the P wave vector shifted rightward by almost 90° (fig 3). All our patients with P pulmonale showed rightward shift of the P wave axis. Juan *et al* also reported that 56% of patients (96/171) with chronic obstructive airways disease had a shift of ≥ +70° in the P wave axis, but only one patient had a shift of > +90°.[5] When the maximum P vector shifts to the right by up to 90°, the components of the P vector reflected in leads II, III, and aVF increase in amplitude. This seemed to be the main mechanism responsible for increased amplitude of the P waves in leads II, III, and aVF in chronic obstructive airways disease. Saha reported that the P axis moved toward the right during the Valsalva manoeuvre, and that the amplitude of the P waves in leads II and III was considerably increased both during the Valsalva manoeuvre and deep inspiration.[6] Saha's report also suggested that verticalisation of the heart was an important factor in the changing of the amplitude and axis of P waves.

In conclusion, there seemed to be little correlation between P pulmonale and right atrial overload. The chest radiographs of the patients with P pulmonale showed a low cardiothoracic ratio, considerable depression of the diaphragm, and straightened right and posterior cardiac borders. Verticalisation of the heart, especially vertical extension of the right atrium, seemed to be a more likely and a more important factor for P pulmonale in chronic obstructive airways disease than the haemodynamic effect of impaired lung function on the right atrium.

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Influence of angiotensin converting enzyme inhibition on pump function and cardiac contractility in patients with chronic congestive heart failure

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Abstract

Eleven patients with coronary artery disease and chronic heart failure were studied before and three months after the angiotensin converting enzyme inhibitor enalapril was added to their frusemide medication. The following were measured: left ventricular pressure and volume with transient occlusion of the inferior vena cava, radionuclide angiography, and hormone concentrations in plasma. As in other reported studies, the clinical condition of the patients improved and their exercise tolerance increased moderately. Addition of enalapril reduced end diastolic and systolic pressure, reduced ventricular volume, and concomitantly increased the ejection fraction. The end systolic pressure-volume relation shifted to the left as it did in a similar animal study. In the animal study unloading by a vasodilator did not induce a leftward shift, so it can be inferred that in the present study unloading combined with a decrease in the angiotensin concentration was instrumental in remodelling the heart. Though unloading was expected to have a beneficial effect on the oxygen supply/demand ratio of the heart, the patients still showed the same drop in the ejection fraction during exercise as they did before treatment with enalapril, and early diastolic filling did not improve. Normally, regression of cardiac dilatation is only found if pump function improves; the present study showed that unloading in combination with angiotensin converting enzyme inhibition reshapes the ventricle without improving intrinsic pump function.

The addition of an angiotensin converting enzyme inhibitor such as enalapril to the conventional treatment of rest, salt restriction, and a diuretic has become an established approach in the treatment of patients with severe congestive cardiac failure. Angiotensin converting enzyme inhibition produces arterial and venous vasodilatation and improves cardiac pump function by unloading the left ventricle. As a result the clinical condition improves and the exercise tolerance[1-3] and life expectancy of the patients increases.[4]

After myocardial infarction the ventricle dilates mainly as a result of slippage of bundles of myocardial cells.[5] Unloading of the heart by angiotensin converting enzyme inhibition reduces ventricular volume,[1 6 7] mainly by lowering the filling pressure, but perhaps also by remodelling, because extensive postinfarct dilatation seems to be reversible. Moreover, it is clear that the observed improvement in exercise tolerance is due not only to better pump function but also to a more efficient distribution of the peripheral circulation. It is a matter of debate whether the pump function improves only because of the unloading and remodelling or because there is also some improvement in the intrinsic function of the cardiac muscle.

Intracoronary injection of angiotensin converting enzyme inhibitors blocked the direct inotropic action of angiotensin II,[8-10] but the long term effect may be to enhance muscle function by improving metabolism and allowing hypoxic muscle cells to recover their contractility.

We studied 11 patients with chronic congestive heart failure with dyspnoea class II-IV (New York Heart Association) before and after three months of treatment with enalapril added to a regimen of diuretics, salt restriction and, in some, digitalis or antiarrhythmic agents. Haemodynamic function was extensively measured. We used on line pressure-volume studies with transient occlusion of the inferior vena cava and radionuclide angiography at rest and during exercise to identify the effects of unloading, of remodelling, and of a possible improvement of myocardial function.

Patients and methods

PATIENTS

Eleven men (aged 48-66 (mean 59)) with chronic congestive heart failure caused by coronary artery disease and myocardial infarction completed the study within a period of 18 months. The patients gave their informed consent and the protocol of the study was approved by the hospital ethics committee. Eighteen patients entered the study but seven did not complete it. Three died suddenly during follow up, one underwent a coronary bypass operation, and three stopped the treatment with enalapril because of side effects.

Inclusion criteria were cardiac failure class II-IV (New York Heart Association) and a left ventricular ejection fraction $<45\%$ at rest, as measured by radionuclide angiography. Stable exercise dependent angina was not a reason for exclusion and patients with mild mitral regurgitation secondary to ventricular dilatation or papillary muscle dysfunction were also not excluded. Exclusion criteria were severe hypertension, myocardial infarction less than four months before, albuminuria, serum creatinine concentrations >150 µmol/l, and valvar or congenital heart disease.

STUDY PROTOCOL

Patients were admitted to the cardiology ward once before treatment and again after three months of treatment. During each admission an exercise test was performed with radionuclide imaging of the left ventricle, followed after one or two days by a right and left heart catheterisation with pressure-volume measurements and balloon occlusion of the inferior vena cava to determine the pressure-volume relations of the left ventricle. Blood samples were taken with appropriate precautions to measure plasma renin and angiotensin converting enzyme activity and concentrations of angiotensin II and atrial natriuretic peptide in the resting state. All prior medication was continued throughout the study and treatment with enalapril was started ($\leqslant$ 20 mg/day). The first dose was given after the haemodynamic tests were completed and the effects were carefully monitored. After three months all variables were measured again.

BIOCHEMICAL MEASUREMENTS

To exclude the effect of physical activity blood samples were taken at 6.00 am before the patients rose. Blood samples for the measurement of angiotensin II and angiotensin converting enzyme activity were collected separately and a combination of EDTA and phenanthroline or of heparin and aprotinin was added, respectively. The samples were kept on ice, centrifuged in a precooled centrifuge, and stored at -70°C. Angiotensin converting enzyme activity was measured spectrophotometrically with a test kit (Paesel, Frankfurt, Germany) that had 15 U/l as its lower limit of reference range. Plasma renin activity was measured by radioimmunoassay of the angiotensin I generated from the α_2 precursor under standard conditions (Baxter, Cambridge, Massachusetts, USA). Enalapril was tested for possible interference in the assay and concentrations of the drug up to 50 µg/ml did not show such effect. The reference range for angiotensin II in normotensive individuals is 0–25 pmol/l plasma (median 18 pmol/l). Normal values of plasma renin activity in ambulant individuals (with unrestricted salt intake) are 1·67 (0·83) µg/l per hour. After extraction on Seppac C18 column (Waters, Bedford, Massachusetts, USA) angiotensin II was measured by a radioimmunoassay with antibodies generated in rabbits. Atrial natriuretic peptide was measured by a radioimmunoassay (Immuno Nuclear, Amsterdam, The Netherlands). The upper limit of the reference range was 68 pg/ml in plasma.

EXERCISE TESTS

The exercise test was performed in combination with radionuclide imaging on a normal upright bicycle ergometer. The workload was increased stepwise from 10 W by 10 W every minute until exhaustion. A Toshiba 40A gamma camera was used to make two radionuclide scintigrams, the former in the 10 minutes immediately before exercise and the latter during the last three minutes of exercise. Red blood cells were labelled in vivo by injecting 750 MBq (20 mCi) technetium-99m. Gated radionuclide angiograms were made in the 40° left anterior oblique position with a 30° caudocranial tilt to obtain optimal separation of the right and left ventricles. The volume of the left ventricle was calculated from the number of ventricular counts and the activity of a blood sample measured simultaneously. Data were collected in a matrix of 64 × 64 pixels.

HAEMODYNAMIC MEASUREMENTS

A 7 F thermodilution Swan-Ganz flow directed catheter was introduced into a femoral vein and its tip was floated into a branch of a pulmonary artery. It was used to measure pressures and cardiac output (by thermodilution and the Fick method). An 8 F Cordis pigtail catheter with a tip manometer was introduced percutaneously into the femoral artery and advanced into the left ventricle. It was used for left ventricular angiography and simultaneous pressure measurements. Left ventricular angiograms were filmed in two directions—the 30° right anterior oblique and the 60° left anterior oblique positions. Later the angiograms were digitised and left ventricular end diastolic and end systolic volumes were estimated by a Philips Analytical Processing Unit system.

The time constant for the exponential decay of pressure (τ) was calculated according to the method described by Weiss *et al.*[11] Subsequently a second 8 F custom made pigtail catheter, with ten electrodes (Webster Labs, Baldwin Park, California, USA),[12 13] was introduced into the left ventricle to measure volume. Its tip was carefully positioned in the apex and a 0·03 mA root mean square 20 kHz alternating current was passed between the most apical electrode and the one close to the aortic valve. Left ventricular volume was calculated on line from the voltages between adjacent pairs of electrodes between the current electrodes[13 14] by an analogue signal conditioner processor (Sigma-5, Leycom, Oestgeest, The Netherlands). Combined with the pressure signal from the tip manometer pressure-volume loops were displayed continuously on an X-Y oscilloscope.

To obtain pressure-volume loops under changing loading conditions a balloon catheter (Meditech, Watertown, Massachusetts, USA) was introduced percutaneously into the femoral vein and the balloon was positioned in the inferior vena cava. When the balloon was inflated with carbon dioxide the venous return to the heart was reduced sufficiently to allow the end systolic pressure-volume relation[15–17] and the relation between dP/dt_{max} and end diastolic volume[18] to be determined.

Absolute values of end diastolic and end systolic volumes measured by conductance catheter were calibrated afterwards against the radionuclide data in eight patients, or, if these data were not available, the volumes were estimated from the ventriculograms.

We used Student's paired *t* test to compare data obtained before and after treatment.

Results

CLINICAL RESPONSE TO TREATMENT

Before treatment two patients were in heart failure class II, eight in class III, and one in class IV. On average they had been in heart failure for 20 months (range 1–96 months). Two patients had moderate angina and two had severe angina. Five patients were treated with digoxin, 10 with frusemide, and three with long acting nitrates. In addition, one patient took flecainide and another amiodarone. All patients were given anticoagulant treatment with coumadin. The cardiac medication was continued without change throughout the study.

Seven patients tolerated a dosage of 20 mg enalapril a day and four were given a daily dose of 10 mg. Eight patients improved clinically but in three the clinical condition remained unchanged. Two of the four patients with angina reported a reduction in episodes of pain.

BIOCHEMICAL RESPONSES

Treatment reduced converting enzyme activity in the plasma from an average of 14·06 U/l to 2·45 U/l ($p < 0.0001$). Plasma renin activity before treatment was high (mean 6·33 μg/l per hour) and it increased to 24·8 μg/l per hour after treatment ($p < 0.005$). Plasma concentrations of angiotensin II were raised before treatment (30·0 pmol/l) and dropped to 10·1 pmol/l after treatment ($p < 0.05$). Initially the plasma concentration of atrial natriuretic factor was considerably raised (189 pg/ml). After three months of treatment it had dropped to 103 pg/ml ($p < 0.05$). Baseline aldosterone concentration was also raised (0·8 μmol/l) before treatment and it fell (but not significantly) to 0·4 μmol/l during treatment.

HAEMODYNAMIC RESPONSES TO ENALAPRIL

Table 1 shows the haemodynamic data. Right atrial pressure, mean pulmonary artery pressure, pulmonary capillary pressure, and left ventricular end diastolic pressure all declined after treatment. Mean aortic pressure also fell. Cardiac index remained practically unchanged. Systemic vascular resistance fell significantly, while the pulmonary vascular resistance also declined but not significantly.

Table 2 shows the volume data obtained by radionuclide angiography. The end diastolic and end systolic volume indices of the left ventricle fell significantly. In nine patients in whom pressure-volume loops could be recorded both before and after treatment, the diastolic pressure-volume relation shifted to the left (fig 1). The ejection fraction at rest increased slightly from 0·24 (0·09) to 0·30 (0·11) ($p < 0.05$).

REMODELLING OF THE VENTRICLE

Pressure-volume loops could be recorded in nine patients. In two (patients 2 and 5) it was not possible to position the conductance catheter in the correct position. Figure 1 shows the shift of the two families of pressure-volume loops, obtained by obstructing the inferior vena cava before and after treatment in patient 4. The diastolic pressure-volume relation was shifted towards the left, which indicates that

Table 1 Haemodynamic function before treatment and three months after treatment with enalapril

Case no	HR (beats/min)	MPRA (mm Hg)	MPAP (mm Hg)	MPCP (mm Hg)	LVEDP (mm Hg)	MAOP (mm Hg)	CI (l/min)	PVR (N.s. m^{-5}) ($\times 10^5$)	SVR (N.s. m^{-5}) ($\times 10^5$)	LVEF (%)	dP/dt_{max} (mm Hg/s)	τ (ms)
						Before treatment						
1	59	15	35	25	20	72	1·5	287	1630	38	659	63
2	111	9	43	30	26	71	2·4	246	1139	30	970	75
3	70	5	21	12	10	101	3·6	92	1152	34	1553	31
4	61	4	16	10	12	84	2·2	130	1752	42	897	66
5	90	7	22	16	15	84	2·8	79	1059	21	—	—
6	48	4	13	11	12	94	2·7	72	1352	38	541	61
7	10	36	35	26	22	81	1·8	205	1648	23	1316	58
8	105	8	20	18	25	70	1·1	77	2384	12	665	71
9	83	14	33	—	20	95	2·3	260	1268	28	1200	60
10	100	5	43	28	25	87	2·3	320	1680	28	1047	62
11	85	5	31	—	25	86	2·8	87	1212	15	1018	40
Mean	83	7·5	28·5	19·6	19·3	84·0	2·3	169	1480	28	987	59
(SD)	21	3·7	10·1	7·4	5·7	9·8	0·6	92	371	15	300	13
						After three months' treatment with enalapril						
1	65	13	29	25	25	72	1·7	112	1532	33	697	78
2	100	5	36	25	25	60	2·9	164	846	35	668	35
3	77	6	17	9	10	105	3·4	88	1100	31	1716	38
4	69	3	17	9	12	92	2·5	153	1575	42	844	59
5	88	7	15	13	13	74	2·1	35	1155	29	—	—
6	61	3	14	7	8	82	3·8	70	803	41	674	35
7	72	5	25	13	14	67	1·6	300	1569	35	938	57
8	92	3	25	18	18	68	2·0	139	1372	19	711	45
9	65	11	28	14	11	58	2·6	282	852	23	1218	55
10	107	3	16	11	14	70	3·0	75	1011	29	1370	27
11	79	2	27	11	25	73	2·3	81	1187	23	1141	55
Mean	80	5·5	22·5	14·1	15·9	74·5	2·5	136	1182	30·9	998	48
(SD)	15	3·4	6·8	5·9	6·1	13·2	0·7	82	280	7·0	337	15
p		0·001	0·05	0·05	0·05	0·05			0·05	0·05		

CI, cardiac index per m^2 body surface area; HR, heart rate; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; MAOP, mean aortic pressure; MPAP, mean pulmonary artery pressure; MPCP, mean pulmonary capillary pressure; MPRA, mean right atrial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Table 2 Responses measured during technetium-99m exercise testing

Case no	*MWL (W)*	*HR rest (beats/min)*	*HR load (beats/min)*	*LVEF rest (%)*	*LVEF load (%)*	*DEF (%)*	*EDVI rest (ml)*	*ESVI rest (ml)*	*SVI rest (ml)*	*HRPP (mm Hg/min) (×10³)*
					Before treatment					
1	40	50	90	18	14	−4	104	85	19	9·90
2	50	100	145	20	19	−1	123	98	25	18·85
3	110	65	105	32	32	0	142	109	33	9 95
4	70	60	100	19	24	5	125	101	24	15·55
5	100	88	135	21	13	−8	189	149	40	24 30
6	110	66	100	38	31	−7	116	72	44	15·55
7	90	100	150	24	15	−9	103	78	25	24·00
8	80	112	142	12	12	0	121	107	14	18 46
9	80	82	120	42	37	−5	121	87	34	22 80
10	60	90	108	19	19	0	153	124	29	14 58
11	120	95	120	21	18	−3	135	107	28	20 40
Mean	83	83	120	24	21	−3	130	102	29	18 58
(SD)	25	19	20	9	8	4	25	22	9	4 41
					After three months' treatment with enalapril					
1	60	70	100	18	—	—	94	77	17	13 50
2	100	90	125	27	23	−4	145	106	39	15 00
3	130	63	100	30	30	0	101	71	30	19 50
4	75	68	110	20	16	−4	64	51	13	21·45
5	110	90	125	23	19	−4	197	152	45	20 00
6	90	64	90	49	36	−13	73	37	36	15 75
7	90	80	135	30	18	−12	92	74	18	21·60
8	125	90	160	22	16	−6	101	79	22	18·40
9	70	75	120	53	47	−6	96	74	22	19 20
10	60	77	130	27	19	−8	101	74	27	19 50
11	130	74	150	27	21	−6	126	92	34	26 25
Mean	90	77	122	30	22	−6	108	81	28	19 10
(SD)	28	10	21	11	12	4	37	22	10	3 52
p				0 05		0 05	0 05	0 01		

DEF, reduction of ejection fraction at rest; EDVI, end diastolic volume per m² body surface area; ESVI, end systolic volume per m² body surface area; HR rest, heart rate at rest; HR load, heart rate during maximal exercise; HRPP, heart rate × pressure product; LVEF rest, left ventricular ejection fraction at rest; LVEF load, left ventricular ejection fraction during maximal exercise; MWL, maximal workload; SVI, stroke volume per m² body surface area.

the passive diastolic properties of the ventricle had changed. This was consistently seen in all patients in whom a pressure-volume loop could be recorded. Figure 2 shows the shifts of the end diastolic volumes of the whole group.

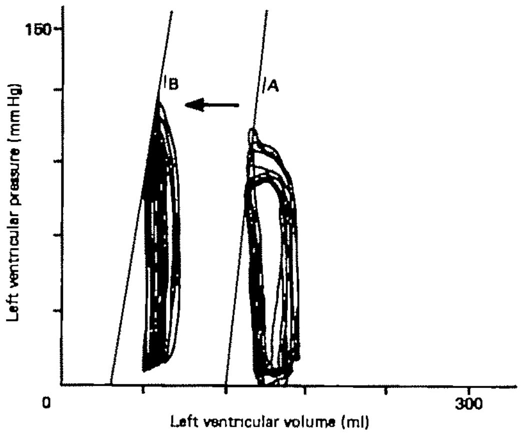

Figure 1 Plots of representative pressure-volume loops during preload reduction by occlusion of the inferior vena cava before (A), and after three months' treatment with enalapril (B). The pressure-volume loops shifted to the left without a change in the slope of the end systolic pressure-volume reaction.

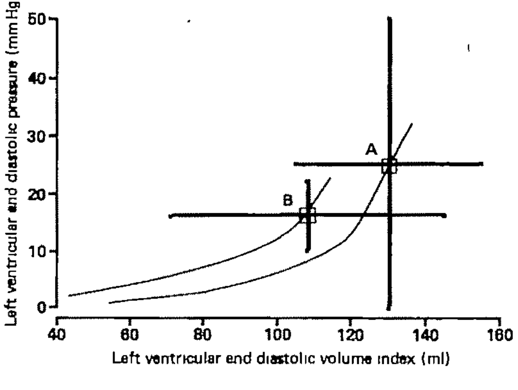

Figure 2 Shift in the end diastolic pressure-volume relation before occlusion of the inferior vena cava in nine patients before (A) and after (B) three months of treatment with enalapril.

EXERCISE TOLERANCE

In seven patients the maximum workload increased, in two it remained unchanged, and in two it decreased after treatment (table 2). On average the maximum exercise capacity increased slightly but not significantly. Heart rate at maximal workload remained practically the same, as did the rate-pressure product. Though eight patients felt that their exercise tolerance had improved, only four increased their maximum rate-pressure product. Three of them did so at the expense of a considerable drop of the ejection fraction during exercise, more than observed before treatment; in the fourth patient the ejection fraction was not measured after treatment.

INDICES OF CONTRACTILITY

On average the values of dP/dt_{max} were below normal before (987 (300) mm Hg/s) and remained unchanged after treatment (988 (337) mm Hg/s). The inferior vena cava could be obstructed effectively in only four patients; in the other five patients in whom pressure-volume loops were recorded the inflation of the balloon did not reduce diastolic pressure and volume either before or after treatment. Figure 3 shows the typical almost parallel shift to the left of the end systolic pressure-volume relation, which indicated almost unchanged end systolic pressure-volume relation. The mean volume intercept shifted from 128 (65) to 55 (24) ml and the slope remained practically the same (0·34 (0·22) mm Hg/ml before and 0·28 (0·10) mm Hg/ml after treatment). The slope of the relation between dP/dt_{max} and end diastolic volume also remained practically unchanged—mean 1·64 (2·31) mm $Hg.s^{-1}.ml^{-1}$ before and 1·23 (0·48) mm $Hg.s^{-1}.ml^{-1}$ after treatment.

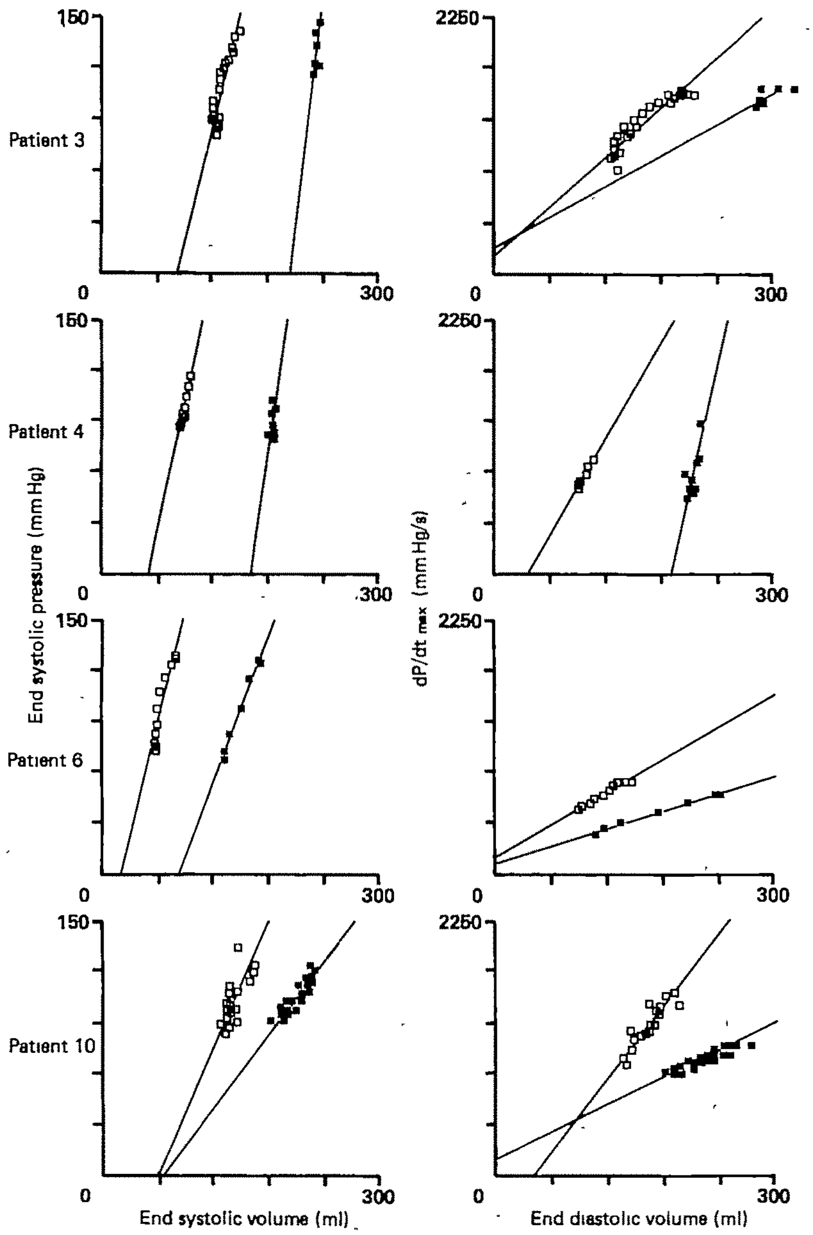

Figure 3 (Left) End systolic pressure-volume relation before and after three months treatment with enalapril in four patients with successful preload reduction by occlusion of the inferior vena cava. (Right) Relation between dP/dt_{max} *and end diastolic volume before and after three months of treatment with enalapril in the same four patients with successful preload reduction by occlusion of the inferior vena cava.*

METABOLIC CONDITION OF THE HEART.

Normally the left ventricular ejection fraction increases during exercise and a drop or even the absence of a rise at maximum workload is taken as a sign of higher overt myocardial ischaemia or hypoxic suppression of contractility caused by a limited coronary reserve. Before treatment the mean ejection fraction for the group decreased from 0·24 (0·09) at rest to 0·21 (0·08) at maximum workload; it fell in seven patients, remained unchanged in three, and increased from 0·19 to 0·24 in one. After treatment the ejection fraction decreased during exercise in nine patients, remained constant in one, and was measured only at rest in one patient. On average, the ejection fraction after treatment dropped from 0·30 (0·11) at rest to 0·22 (0·12) at maximum workload. In seven patients the fall in the ejection fraction during exercise became more pronounced, and in three of these patients the maximal rate-pressure product increased. The only patient whose ejection fraction increased during exercise and who attained a rate-pressure product of 15·5 ($\times 10^3$) mm Hg/min, exercised to a rate-pressure product of 21·4 ($\times 10^3$) mm Hg/min after treatment but his ejection fraction fell.

Because relaxation in early diastole is an active, energy dependent process, the negative peak dP/dt and the time constant τ of the exponential decay of pressure immediately after a negative peak dP/dt are both regarded as indices of the metabolic condition of the heart muscle. There was little change in the peak negative dP/dt (903 (190) mm Hg/s, and 891 (229) mm Hg/s) (NS). The value of τ also did not change significantly after treatment (table 1).

Discussion

Earlier studies showed that addition of an angiotensin converting enzyme inhibitor to the frusemide treatment of patients with severe cardiac failure improved their clinical condition, exercise tolerance, and prognosis.[4 19 20] After three months of treatment the left ventricle was smaller and the heart produced the same cardiac output at a lower filling pressure against a lower aortic pressure.[1 5] The present study confirms these results. Biochemical data show that the inhibition of the angiotensin converting enzyme was effective in all patients and that the angiotensin II and atrial natriuretic concentrations were reduced. Most patients felt better and their maximum workload increased. As a result of the treatment the pressure-volume loops shifted to the left and the recordings showed that the support structure of the ventricle had changed. Figure 1 shows that the reduction of diastolic ventricular volume achieved by lowering end diastolic pressure was much more important than the slight changes induced by an acute reduction of pressure of the same magnitude. This shows that the collagen support structure of the heart has indeed been reshaped.

A shift of the diastolic pressure-volume relation of the human left ventricle under the influence of enalapril has not been reported before, but similar results have been obtained experimentally by treating rats with chronic large myocardial infarctions with captopril.[21] Unloading the heart with a predominantly arterial vasodilator, hydralazine, did not produce such an effect.[22] From this it can be inferred that the ventricle is reshaped only because unloading is combined with a reduction of the angiotensin concentration. This conditional role of a reduction of angiotensin is supported by the results of experimental studies that point to a crucial role of such reduction in changing the collagen structure of the heart. A comparison of the effects of different types of hypertension and of angiotensin converting enzyme inhibition on rat hearts showed that renovascular hypertension induced cardiac hypertrophy with a higher collagen content than low renin hypertension caused by infrarenal banding.[23] Regression of hypertrophy with angiotensin converting enzyme inhibition is accompanied not only by a reduction of collagen content but also by a considerable change in the ratio of type I and type III collagen.[24,25]

Because the support structures in the heart were reshaped, the collagen tethers between bundles of cardiac fibres must first have been dissolved and later reformed.[26] Acute unloading shifts the diastolic pressure-volume relation only slightly to the left,[15] but in combination with the reconstruction of collagen tethers such a shift to a lower volume can be repeated until an appreciably lower volume is reached. This implies that remodelling of the heart will occur only if the heart is unloaded while the plasma concentrations of angiotensin II are simultaneously reduced. In an experimental study, treatment with a vasodilator that unloads the heart but activates the renin-angiotensin-aldosterone system did not reduce heart size.[22]

In the acute experiment a leftward shift of the end systolic pressure-volume relation is usually interpreted as a sign of improved contractility.[15,27,28] The same is true for the relation between dP/dt_{max} and end diastolic volume,[18,27] but is such interpretation still correct in a long term study in which the ventricle is considerably remodelled and reduced in size? We found no additional evidence of an improvement of intrinsic contractile function in this study. A direct positive effect of enalapril would have been unlikely, because angiotensin II was weakly inotropic in isolated cardiac muscle[8-10] and angiotensin converting enzyme inhibitors had a weakly negative inotropic action.[29] Contractile function might have improved, however, by improvement in the heart's metabolism. Coronary reserve is usually reduced in cardiac failure and regional hypoxia of the muscle may add to the problem of cardiac failure caused by previous infarctions. The unloading of the heart may have a beneficial effect on its metabolism by reducing oxygen consumption, but lowering coronary perfusion pressure may have an opposite effect. The present data on reduction of ejection fraction during exercise suggest that the net effect of the unloading treatment on the oxygen balance was negligible or in some patients even slightly negative. Nor did the data on ventricular relaxation indicate an improvement in cardiac metabolism. So there seems little reason to suppose that treatment with an angiotensin converting enzyme inhibitor in this group of patients improved intrinsic muscle function, despite the leftward shift of end systolic pressure-volume relation and the relation between dP/dt_{max} and end diastolic volume. The improvement of pump function seems to be solely the result of the remodelling of the heart, without recruitment of hitherto hypoxic fibres.

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Alcohol ablation of atrioventricular conduction

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Abstract

Transcoronary ablation of atrioventricular conduction by dehydrated alcohol was attempted in 14 patients with refractory atrial arrhythmias. Alcohol (0·5 or 1·0 ml) was delivered after selective catheterisation of the atrioventricular nodal artery in the 10 patients in whom the artery could be identified by cineangiography. The other four patients underwent electrical ablation when the nodal artery could not be catheterised. Temporary atrioventricular block induced by dilute contrast and cold saline (0·9%) confirmed that the catheter was in the correct position before the alcohol was delivered. In all 10 patients complete atrioventricular block developed after alcohol ablation. The block persisted in all four patients given 1·0 ml alcohol but not in four of the six given 0·5 ml. The mean (SD) creatine kinase (MB fraction) at four to six hours after ablation was 76·5 (49·5) IU after 1·0 ml and 75·5 (43·1) IU after 0·5 ml alcohol (normal < 20 IU). The overall success rate of alcohol ablation in the whole group on an "intention to treat" basis was 43%. The procedure was a technical success in six of the 10 patients in whom the nodal artery was identified.

Transcoronary alcohol ablation of atrioventricular conduction should be considered in patients in whom electrical techniques have been unsuccessful.

Closed chest electrical ablation of atrioventricular conduction is now an accepted treatment for atrial arrhythmias that are refractory to drugs. Conventional high energy capacitor discharge, however, has several disadvantages. The success rate is only moderate and serious complications have been reported.[1] Because the shock is painful, the patient needs general anaesthesia and ablation often needs to be repeated.

These drawbacks have led to alternative techniques being developed. The initial results with radiofrequency energy and low energy direct current ablation were encouraging.[2 3] A transcoronary approach has been used to treat ventricular tachycardia and atrial arrhythmias.[4 5] We investigated the feasibility, safety, and clinical value of transcoronary alcohol ablation of atrioventricular conduction in patients who would otherwise have been considered for conventional electrical ablation.

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Patients and methods

PATIENTS

We studied all 14 patients (mean age 64 (range 54–75); nine men) admitted for ablation of atrioventricular conduction between November 1989 and April 1990. Table 1 summarises the clinical characteristics of the study patients. Four patients had evidence of structural cardiac pathology: in two the mitral valve had been replaced because of rheumatic disease and two had haemodynamically insignificant mitral valve prolapse. The arrhythmia was atrial flutter or fibrillation in 12 patients, one patient had atrioventricular nodal re-entry tachycardia, and one had focal atrial tachycardia. Symptoms had been present for 1–60 years (median 3·5 years). These patients had been refractory to or intolerant of a mean (SD) of 4·4 (1·8) antiarrhythmic drugs, including amiodarone in 11. In three patients an earlier attempt at electrical ablation had been unsuccessful. The protocol was approved by the St George's Hospital ethics committee and all patients gave written consent for the procedure after the possible risks and benefits and its experimental nature had been explained.

EXPERIMENTAL PROTOCOL

For the initial coronary angiographic examination, we used the Judkins approach to identify the atrioventricular nodal artery. Multiple views of the dominant artery were taken to enhance the identification of the nodal artery before ablation. The ablation procedure was undertaken with the patients in a fasted, premedicated, and midly sedated state. A 6F bipolar wire was placed in the right ventricular apex to serve as a temporary pacemaker and a 6F tripolar wire was positioned to record the largest bipolar His potential. A standard 8F or 9F angioplasty guiding catheter was positioned in the ostium of the coronary artery which gave rise to the atrioventricular nodal artery. 10 000 units of heparin and 250 μg of glyceryl trinitrate were administered prophylactically by intracoronary injection. The atrioventricular nodal artery was selectively cannulated with a 2·2F infusion catheter (Target Therapeutics Tracker-18 Hi-Flow), which was manipulated over a 0·013 inch steerable guide wire (Target Therapeutics Flex-Tip) (fig 1). The catheter was advanced as far as possible to wedge within the artery. Warm dilute contrast was then injected to exclude the presence of backflow into the main artery. If backflow occurred the catheter was remanipulated and the injection repeated. We confirmed that the catheter

Table 1 Clinical characteristics of patients at entry

Patient	*Age/sex*	*Arrhythmia*	*Duration (yr)*	*No of anti-arrhythmic drugs*	*Symptoms*	*Other cardiac diagnoses*	*Previous ablation*
1	67/M	AFL	8	7	P, CP, D	MVP	No
2	67/M	PAF	5	4	P, D	None	No
3	62/M	PAF	3	6	P, D	MVP	No
4	54/M	AF	5	3	P, D	MVR	No
5	70/F	AVNRT	60	5	P, PS	None	No
6	75/M	AT	2	2	P, D	None	No
7	62/F	PAFL	2	4	P, D, PS	None	No
8	64/F	AF	3	3	P, D	MVR	Yes
9	63/M	AFL	4	1	P, S	? VT	No
10	60/M	PAF	3	4	P, D, PS	None	Yes
11	59/F	PAF	11	4	P, CP, D, PS	None	No
12	63/M	AFL	1	7	D, PS	None	No
13	59/M	AFL	2	6	P, D, PS	None	No
14	70/F	AF	10	6	P, D, PS	None	Yes

AF, persistent atrial fibrillation; AFL, persistent atrial flutter; AT, atrial tachycardia; AVNRT, atrioventricular nodal re-entry tachycardia; CP, chest pain; D, dyspnoea; MVP, mitral valve prolapse; MVR, mitral valve replacement; P, palpitation; PAF, paroxysmal atrial fibrillation; PAFL, paroxysmal atrial flutter; PS, presyncope; S, syncope; VT, ventricular tachycardia.

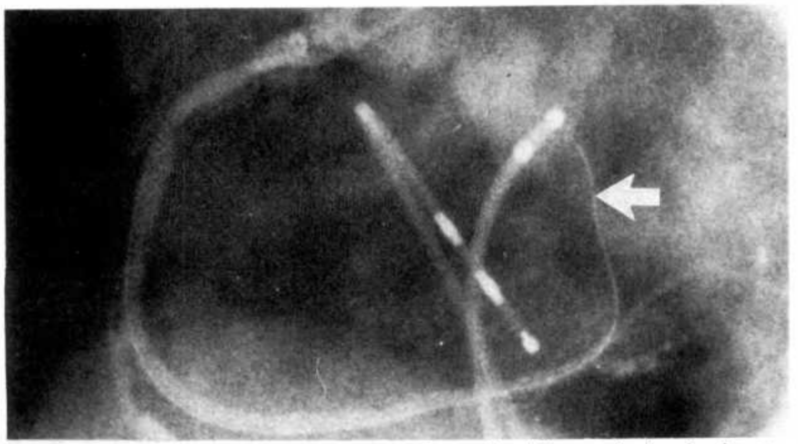

Figure 1 A right coronary angiogram in the left anterior oblique projection showing an 0·013 inch guide wire (arrow) manipulated deep into the atrioventricular nodal artery.

was correctly placed by injection of 2–10 ml cold saline (0·9%). If this caused a definite transient complete heart block we injected 0·5 or 1·0 ml of dehydrated alcohol over one second and then 1·0 ml of saline. Patients 2, 3, 4, and 14 were given 1·0 ml and patients 5 and 7–11 0·5 ml. The reasons why we changed the dose will be discussed later.

All patients were monitored on the cardiac ward for 24 hours after the procedure. If necessary a permanent pacemaker was inserted within 48 hours. All patients had cross sectional echocardiography with a Diasonics CFM 500 or a Hewlett Packard Sonos 1000S before and within three days of the procedure. Creatine kinase (MB fraction) activity was measured in blood samples taken four to six hours after injection of alcohol.

Results

IDENTIFICATION OF THE ATRIOVENTRICULAR NODAL ARTERY

In 10 patients the artery supplying the atrioventricular node was identified on the initial cineangiogram. In nine it originated from the right coronary artery (one of them had a dual arterial supply) (fig 2) and in one patient it arose from the left circumflex artery. The artery could not be identified in four patients, two of whom had a left dominant anatomy. In the four patients in whom the vessel could not be visualised during screening it was identified on the developed films.

CATHETERISATION OF THE ARTERY SUPPLYING THE ATRIOVENTRICULAR NODE

We successfully cannulated all 11 arteries (in 10 patients) that were visible on the angiograms and confirmed the position of the catheter by infusion of contrast and cold saline. The injection of dilute contrast led to varying degrees of atrioventricular block in all patients, but at that time we believed that it was necessary to inject cold saline to be certain that the correct vessel had been catheterised. Injection of cold saline into the nodal artery produced transient complete atrioventricular block in all patients. Incomplete block, notably slowing of the ventricular response in patients with atrial fibrillation or flutter, was seen when contrast or cold saline were injected into vessels which ran close to the nodal artery. Because the coronary artery went into spasm during three early procedures we reduced the volume of cold saline injected from 10 ml to 2 ml. Not surprisingly we could not catheterise the atrioventricular nodal artery in any of the four patients in whom the artery could not be identified on cineangiography, though it was probably entered with a guide wire in one case.

RESULTS OF ALCOHOL INJECTION

Table 2 shows the initial results of the ablation procedure and table 3 shows the long term outcome. In all 10 patients complete atrioventricular block developed immediately after the injection of alcohol. All four patients in whom 1·0 ml alcohol was injected were still in complete heart block 4–7 months after the procedure. So too were patients 9 and 11 who were given 0·5 ml alcohol. Atrioventricular conduction returned in four patients who were given 0·5 ml of alcohol. One (patient 8) of them had two separate ablation procedures. Patient 5, who had atrioventricular nodal re-entry tachycardia, remained well with no clinical or inducible tachycardia. Patient 7, in whom conduction resumed 30 minutes after ablation, underwent a repeat procedure four days later. This was unsuccessful because the nodal artery was occluded. Two attempts at electrical ablation were also unsuccessful in this patient and she is awaiting surgical ablation. Patient 8, who had dual nodal arteries, had a further injection of 0·5 ml into the second artery after conduction recurred 24 hours after the initial attempt

Table 2 Results of alcohol albation

Patient No	*AVNA seen on angiogram*	*Presumed vessel of origin**	*AVNA seen on screening*	*AVNA catheterised*	*Dose of alcohol (ml)*	*AV block with alcohol*
1	No	R	No	No	None	—
2	Yes	R	Yes	Yes	1·0	Yes
3	Yes	R	Yes	Yes	1·0	Yes
4	Yes	R	Yes	Yes	1·0	Yes
5	Yes	R	No	Yes	0·5	Yes
6	No	L Cx	No	No	None	—
7	Yes	L Cx	Yes	Yes	0·5	Yes
8†	Yes	R	Yes	Yes	0·5 + 0·5	Yes + yes
9	Yes	R	Yes	Yes	0·5	Yes
10	Yes	R	No	Yes	0·5	Yes
11	Yes	R	No	Yes	0·5	Yes
12	No	L Cx	No	No	None	—
13	No	R	No	No	None	—
14	Yes	R	No	Yes	1·0	Yes

*When the atrioventricular nodal artery could not be seen on the developed films, it was assumed to originate from the vessel supplying the posterior descending artery

†This patient underwent two alcohol ablation procedures.

AV, atrioventricular, AVNA, atrioventricular nodal artery, L Cx, left circumflex artery; R, right coronary artery

Table 3 Follow up results of all patients

Patient No	*Peak CK MB (IU/l)* after alcohol*	*Repeat procedures*	*Current state*	*Follow up (mnth)*	*Current antiarrhythmic medication*
1	—	EA	AV block	7	None
2	48	None	AV block	7	None
3	35	None	AV block	7	None
4	146	None	AV block	6	None
5	131	None	CR, NT	6	None
6	—	FEA	AT	6	Amiodarone
7	102	FAA, FEA	SR, PAFL	5	Flecainide
8†	62 and 15	FAA, FEA	AF	4	None
9	100	None	AV block	5	None
10	‡	None	CR	5	Digoxin
11	43	None	AV block	5	None
12	—	EA	AV block	4	None
13	—	FEA	SR, PAFL	4	Sotalol
14	77	None	AV block	4	None

*Normal < 20 IU/l.

†This patient underwent two alcohol ablation procedures.

‡The creatine kinase results for patient 10 are not available owing to a laboratory mishap.

AF, atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular; CR, conduction returned; CK MB, creatine kinase MB fraction; EA, electrical ablation; FAA, failed alcohol ablation; FEA, failed electrical ablation, NT, no tachycardia; PAFL, paroxysmal atrial flutter, SR, sinus rhythm.

(fig 2). Unfortunately, this attempt also failed because conduction resumed after 48 hours. A further attempt was thwarted by both vessels being occluded. Atrioventricular conduction returned after nine days in patient 10 who is now awaiting a further attempt at electrical ablation. The chances that an ablation procedure would produce long term heart block were significantly improved ($p < 0\cdot05$) when 1·0 ml of alcohol was given (Fisher's exact test).

The injection of alcohol was well tolerated by all patients though most reported minor transient chest discomfort immediately after the injection. All patients were monitored for 24 hours after the procedure; none showed any new arrhythmias. The echocardiographic ejection fraction did not change in patients given alcohol and there were no new segmental wall motion abnormalities. The mean (SD) creatine kinase (MB fraction) concentrations measured four to six hours after each alcohol injection were 76·5 (49·5) IU for patients given 1·0 ml alcohol and 75·5 (43·1) IU for those given 0·5 ml (normal range < 20 IU). The mean serum concentration of creatine kinase MB in patients in whom long term complete heart block occurred after alcohol was 74·8 (42·5) IU and in those in whom conduction recovered it was 77·0 (50·0) IU. Unfortunately the enzyme results of patient 10 are unavailable owing to a laboratory mishap.

ESCAPE RHYTHMS

Four to six weeks after the procedure all patients in whom alcohol ablation had been successful showed stable escape rhythms—RR interval 1272 (160) ms and QRS duration 97 (25) ms.

COMPLICATIONS

In two patients ventricular fibrillation developed when contrast was injected into the right coronary artery before the infusion catheter was introduced. Prompt defibrillation restored sinus rhythm immediately and the procedure was successfully completed in both patients. Coronary artery spasm developed in three patients after injection of cold saline. Two of these had been given intracoronary glyceryl trinitrate. The ensuing hypotension and ST elevation resolved rapidly with further nitrate. The two patients in whom spasm developed and who did not go on to receive alcohol showed no increase in cardiac enzymes. One patient had evidence of a small dissection of the right coronary artery seen on the final injection of contrast. This was not associated with any short or long term adverse effects.

Discussion

We showed that alcohol ablation of atrio-

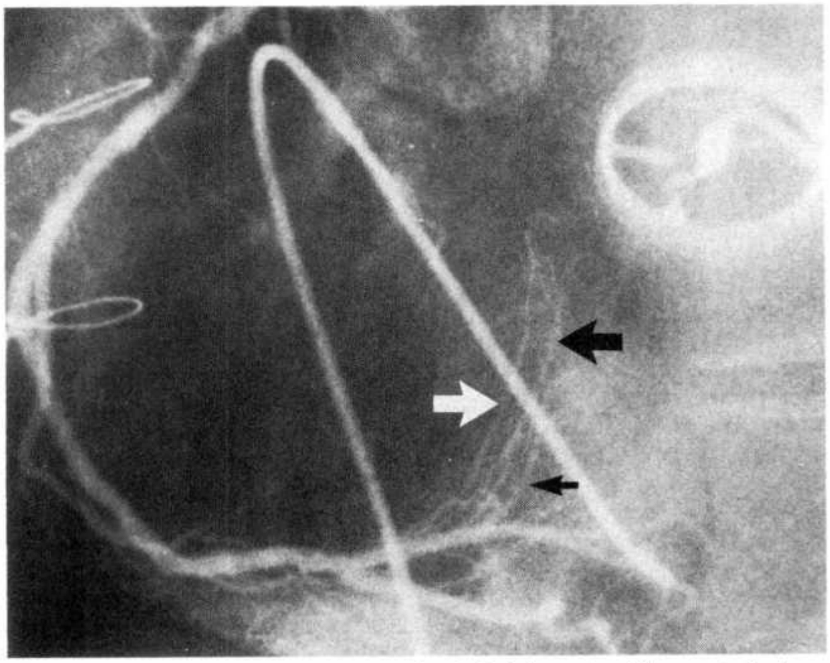

Figure 2 A right coronary arteriogram taken in the left anterior oblique projection in a patient (case 8) who had dual nodal arteries. The proximal artery (white arrow) was cannulated at the first ablation attempt and was occluded at a later study. The distal artery (black arrow) was entered and alcohol injected but atrioventricular conduction returned. A third attempt was made but both main nodal vessels were occluded and injection of cold saline into the third artery (small arrow) had no effect on conduction.

ventricular conduction is a safe and practical procedure in most patients

SUCCESS OF ALCOHOL ABLATION

The atrioventricular nodal artery must be identified on the initial coronary angiogram before it can be cannulated. We do not recommend speculative attempts unless a suitable candidate vessel has been seen. Inability to see the nodal artery during screening, however, did not reduce the likelihood of successful cannulation if the vessel was identified on the original developed films. In all patients in whom the nodal artery was cannulated complete heart block developed when alcohol was injected, but in three atrioventricular conduction returned and their symptoms continued. The ablation procedure in the patient with nodal re-entry was technically unsuccessful but the clinical outcome was satisfactory. The procedure was significantly more successful when 1·0 ml rather than 0·5 ml alcohol was used. The initial choice of a dose of 1·0 ml was based on the reports of Brugada *et al.*[5] In an attempt to minimise myocardial damage we reduced the dose but this led to reduced success with no change in enzyme release and so we returned to 1·0 ml for the last patient in the series. Enzyme release was not related to the amount of alcohol injected or the technical success of the procedure.

MECHANISM OF ACTION OF ALCOHOL ABLATION

Studies of patients with inferior myocardial infarction and experimental work in dogs showed that simple occlusion of the nodal artery does not result in major long term structural or electrophysiological abnormalities in the node.[6-8] This accords with our observation that the nodal vessels were occluded proximally in the two patients restudied after conduction had recurred. Because the atrioventricular node, in common with other areas of the conducting system, is more resistant than the myocardium to ischaemia it must have an adequate collateral blood supply from atrial and septal vessels.[9 10] The instantaneous block produced by alcohol suggests a direct toxic effect upon nodal tissue. The fact that the release of creatine kinase is independent of the dose of alcohol suggests that the normal myocardial tissue supplied by the nodal artery is fully infarcted by the toxic effects of even the lower dose of alcohol. The specialised conducting tissue also seems to be more resistant than the myocardium to the effects of alcohol. Slow infusion of alcohol into renal arteries caused ischaemic damage secondary to vascular sludging by denatured red cells but our rate of alcohol delivery was rapid enough to subject all areas supplied by the nodal artery to very high concentrations of alcohol.[11] One possible explanation for the failures with the lower dose was that the alcohol was not long enough in contact with the node before it was flushed out either actively or by resumption of flow after removal of the catheter. It might be better to leave the catheter wedged in the artery for longer and increase the time that the nodal tissue is bathed in alcohol. This would probably cause a little extra myocardial damage because much of the muscle supplied by the vessel is likely to be jeopardised by the initial toxic effects. The ideal dose, concentration, and flow rate of alcohol for maximum efficacy and safety have yet to be determined.

The lesions produced by intracoronary alcohol have mainly been studied after injection into left ventricular branches in animals. Inoue *et al* reported the results of infusion of 100% alcohol using occlusive cannulation into a diagonal branch of the left anterior descending artery in eight dogs.[12] This produced predominantly focal discrete transmural infarction but in two dogs patchy or diffuse lesions developed. In the absence of histological information it is not possible to predict the exact morphology of the lesions produced in our patients. The possibility that alcohol infusion induces irregular lesions raises concern about new ventricular arrhythmias developing, especially as the nodal artery may supply a small area of the upper interventricular septum.

The escape rhythms in the patients who had alcohol ablation of the ventricular node were predominantly narrow complex but one patient showed a left bundle branch block configuration and another showed incomplete right bundle branch block. This is consistent with previous studies that showed that blood was supplied to the His bundle and its branches by a continuation of the nodal artery.[13]

COMPARISON WITH OTHER TECHNIQUES OF ABLATION

In this prospective study, alcohol ablation was a technical success, on the basis of an "intention to treat", in six (43%) out of 14 patients. In patients in whom the nodal artery could be identified alcohol ablation was technically successful in 60% and a clinical success in 70%. There is good reason to believe that the results will improve with further development of the technique. Certainly the procedure is limited to patients with identifiable arteries and no important coronary artery disease of the dominant vessel. de Swart *et al* who used similar doses in most of their patients reported complete success in five of 10 patients, modification of conduction in two, and in three coronary artery disease or failure of visualisation of the nodal artery precluded alcohol ablation.[14] The technique avoids the need for general anaesthesia and the risks of barotrauma associated with conventional high energy ablation.

Success rates with other techniques, however, are higher. When long term complete heart block was regarded as the end point, conventional ablation was successful in 65% of 354 patients.[1] Successful low energy direct current ablation was reported in 79–100% and radiofrequency energy was successful in 56–71% of patients.[3 15 16]

The release of cardiac enzymes after alcohol ablation is appreciably higher than has been reported for other methods of ablation. Brugada *et al* reported a mean aspartate aminotransferase of 89 U (normal < 40) in six of their patients; one patient who sustained an inferior wall infarction was excluded from this analysis.[5] Direct comparison of peak creatine kinase MB concentrations after conventional ablation (22–40 IU) and alcohol ablation (76 IU) is hampered because different assay methods were used.[2 17] Enzyme release was negligible after low energy and radiofrequency ablation. The large release of enzymes after alcohol ablation is disturbing; however, the nodal artery supplies only a small area of muscle and echocardiographic study did not show any new abnormalities. We are currently studying whether there is a more rapid or complete release of enzymes after an alcohol injury than after other insults.

The occlusion of the nodal artery after alcohol unfortunately precludes repeated attempts at ablation except when, unusually, there are dual arteries. With other techniques subsequent procedures are possible if conduction returns.

COMPLICATIONS

The two cases of ventricular fibrillation occurred before the infusion catheter was introduced and were simply secondary to injection of contrast material. Coronary artery spasm followed injection of cold saline in three patients and was associated with significant haemodynamic disturbance. This complication can be minimised by an initial injection of warm dilute contrast into the selected candidate vessel. This will usually cause block if the catheter is correctly positioned and if any backflow into the main artery is seen the catheter can be repositioned. Atrioventricular block can be achieved with a much smaller dose of cold saline than has been previously reported; 1–2 ml is sufficient if the catheter is properly wedged within the artery.[5] We have more recently abandoned the use of cold saline if dilute contrast produces convincing evidence that the correct vessel has been catheterised. A combination of these precautions and prophylactic intracoronary nitrates should minimise the risk of spasm. Backflow of alcohol if the infusion catheter is not completely wedged can be disastrous. Brugada *et al* reported the dangers of attempted repeat ablation when, though the main vessel seems to be patent, occlusion of the distal segments causes backflow.[5]

Conclusions

This prospective study of the use of alcohol ablation showed the feasibility of the technique. The modest success rate, concern about the release of cardiac enzymes, and the potential for serious complications suggest that this technique should probably be reserved for patients in whom other ablative treatments have failed. Alcohol ablation, which began as a treatment of last resort for ventricular tachycardia, should now be seriously considered before the more radical approach of surgical interruption of atrioventricular conduction. Further study to determine the optimal dose, concentration, and contact time between the node and alcohol is likely to improve the results. If backflow of alcohol or cold saline is scrupulously avoided, perhaps by use of a balloon occlusion catheter, the risks of significant complications may be reduced.

We thank Dr Albert Fenech for his permission to report the details of one of his patients

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Balloon atrial septostomy under echocardiographic control: six years' experience and evaluation of the practicability of cannulation via the umbilical vein

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Abstract

Balloon atrial septostomy was undertaken under cross sectional echocardiographic control in 63 consecutive infants: in no case was fluoroscopic imaging required. The procedure was performed in the cardiac catheterisation laboratory, ward side room, or at the bedside in the neonatal intensive care unit. Catheterisation via the umbilical vein was attempted in 37 infants aged <48 hours old and was successful in 27. No complication was clearly attributable to the procedure though two infants died. A nine day old child died from disseminated intravascular coagulation the day after septostomy by the iliofemoral route and another, aged nine days, died of necrotising enterocolitis which had developed when he was eight days old, after umbilical catheterisation at eight hours.

Balloon atrial septostomy is a safe and easy procedure under cross sectional echocardiographic imaging control. Catheterisation via the umbilical vein was safe, easy to perform, and is appropriate in infants aged <48 hours.

Balloon atrial septostomy remains an important palliative procedure in many infants with cyanotic congenital cardiac conditions.[1] After its introduction in 1966[2] the procedure was performed under the control of fluoroscopic imaging. This form of imaging does not show the intracardiac structures directly and because the catheter has to be manipulated in relation to the anatomical landmarks on the image the risk of damage to the related intracardiac structures is increased.[3] Recently it has become possible to perform septostomy under the imaging control of cross sectional echocardiography.[4] This shows clearly the intracardiac anatomy and the precise position of the catheter tip, which reduces the risk of inadvertently damaging the mitral valve or other intracardiac structures. Not all workers accept ultrasound as the most appropriate imaging control for all patients.[5]

Catheterisation via the umbilical vein allows a catheter to be inserted easily and quickly into the heart but it does not permit much catheter manipulation. Because during balloon atrial septostomy the catheter requires only slight manipulation to enter the left atrium and because most infants undergoing septostomy do not need a formal catheter investigation the umbilical vein may provide a suitable route.

Earlier studies of cross sectional echocardiographic imaging in balloon atrial septostomy were small[4] or compared this technique with that of fluoroscopic imaging.[6] We are not aware of any long term study of the routine use of echocardiographic imaging control for atrial septostomy or of the assessment of the use of the umbilical vein for catheterisation. For six years we have used the umbilical vein and echocardiographic imaging control for balloon atrial septostomy.

Patients and methods

Sixty three patients underwent balloon atrial septostomy at the Royal Hospital for Sick Children, Glasgow, between September 1984 and September 1990. Initially septostomy was not routine in those with univentricular heart with absent right atrioventricular connection (tricuspid atresia) but this policy changed and more septostomies were carried out in the later period of the study. At the time of septostomy 18 patients were <24 hours old, 30 were 24–48 hours old, and 15 were > two days old. Birth weights ranged from 1·4 to 4·7 (mean 3·3) kg.

We used the procedure to palliate various congenital cyanotic conditions: transposition of the great arteries (46), pulmonary atresia (seven), tricuspid atresia (seven), hypoplastic left heart syndrome (one), and other complex congenital cardiac anomalies (two) with or without transposition of great arteries. At the time of septostomy 34 patients were being treated with a prostaglandin infusion.

The underlying cardiac defect was diagnosed on cross sectional echocardiography, with the addition of colour Doppler flow mapping from January 1987. At first we used commercial ATL equipment (Advanced Technology Laboratories) and later a Vingmed CFM 700, both with a 5 MHz transducer.

We catheterised the umbilical vein or iliofemoral vein with a 5F Fogarty atrial septostomy balloon catheter (Edwards laboratories). When we used the umbilical venous route we cleaned the stump and transected it near the skin. The catheter tip was inserted directly into the lumen of the umbilical vein and gently

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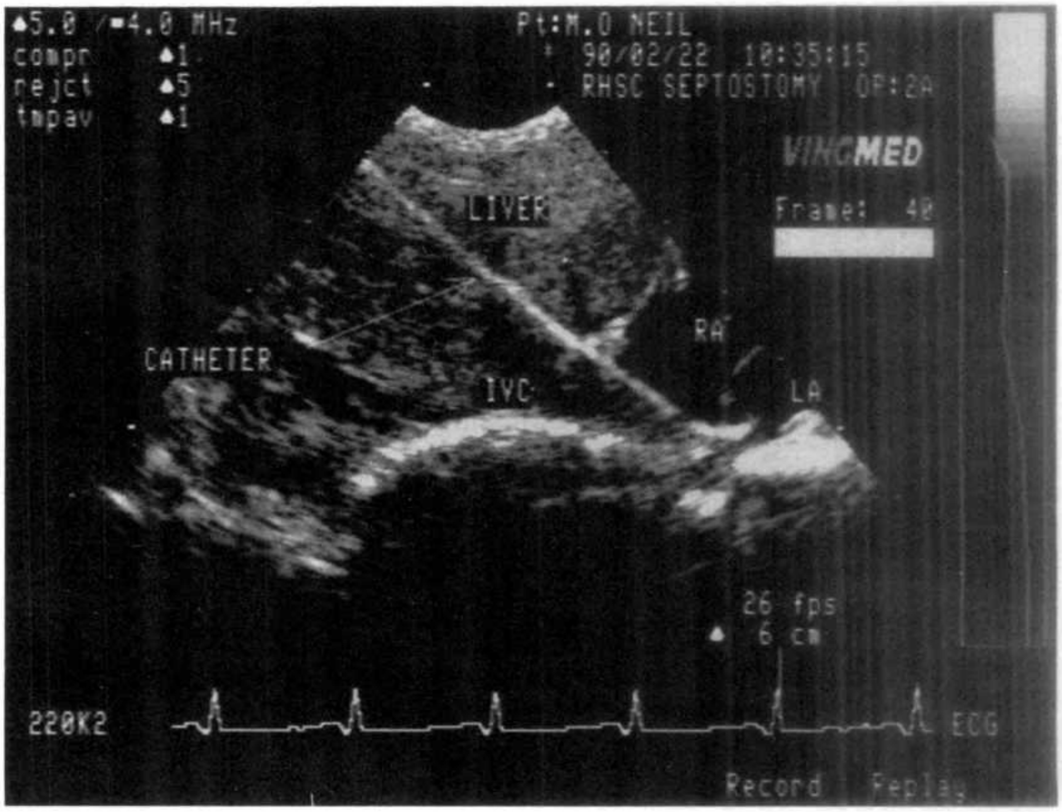

Figure 1 Modified subcostal view showing a clear image of the catheter with the umbilical vein as route of entry for the catheter. The catheter traverses the ductus venosus and enters the right atrium and left atrium through a patent foramen ovale. Parts of the left atrium, interatrial septum, and a pulmonary vein are also visible.

advanced and rotated if we encountered resistance. To get the catheter into the inferior vena cava we sometimes had to press gently on the subxiphoid region or use the central wire to straighten the tip of the catheter. We could see the catheter passing through the liver (fig 1) but the image was not of practical value when we had difficulty passing the catheter through the ductus venosus. If the catheter could not be passed easily into the heart the procedure was not prolonged and the femoral route was used. At the end of the procedure the stump was sutured. No antibiotics were administered before or after the procedure. When the femoral route was used the catheter was introduced either percutaneously through a French gauge 7 sheath or, if this was unsuccessful, by cut down. We attempted to catheterise the umbilical vein in those infants who were less than 48 hours old; we succeeded in 27 and failed in 10. The iliofemoral route was used electively in 26 patients, 11 of whom were less

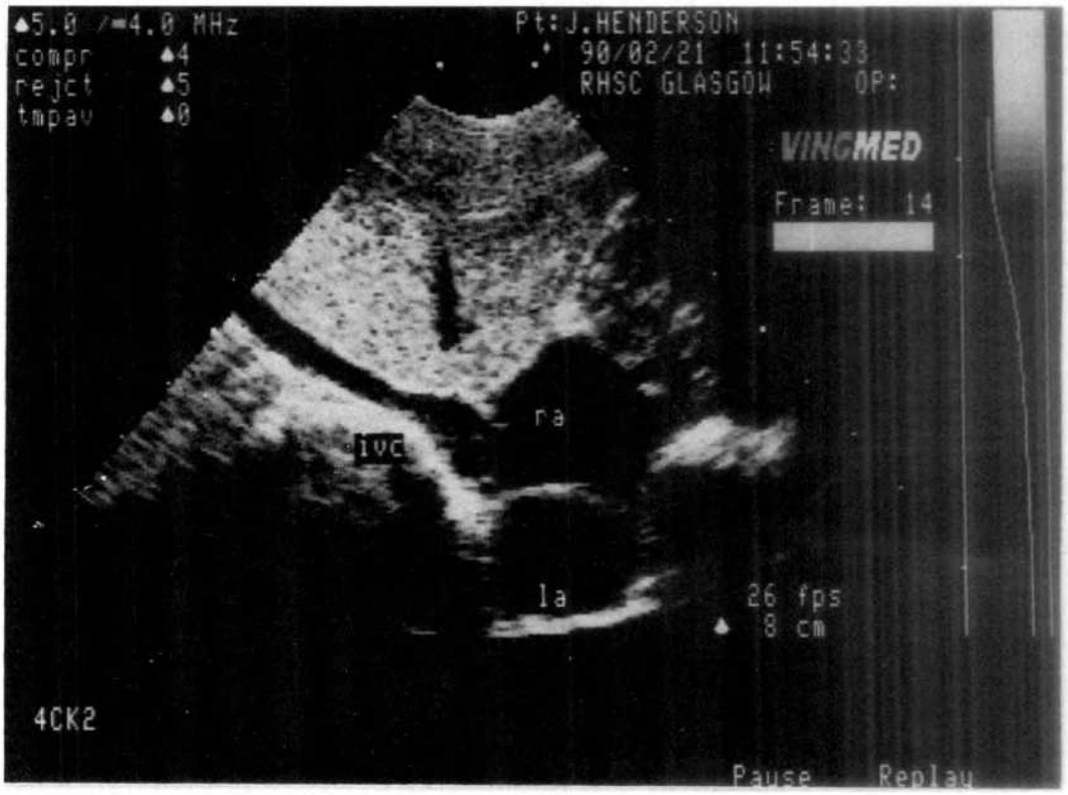

Figure 2 Subcostal four chamber view obtained by medial and superior angulation of the transducer showing the inferior vena cava (ivc), right atrium (ra), interatrial septum, and left atrium (la) in one plane. This view facilitated manipulation of balloon catheter. Both atrioventricular valves and the interventricular septum can also be seen.

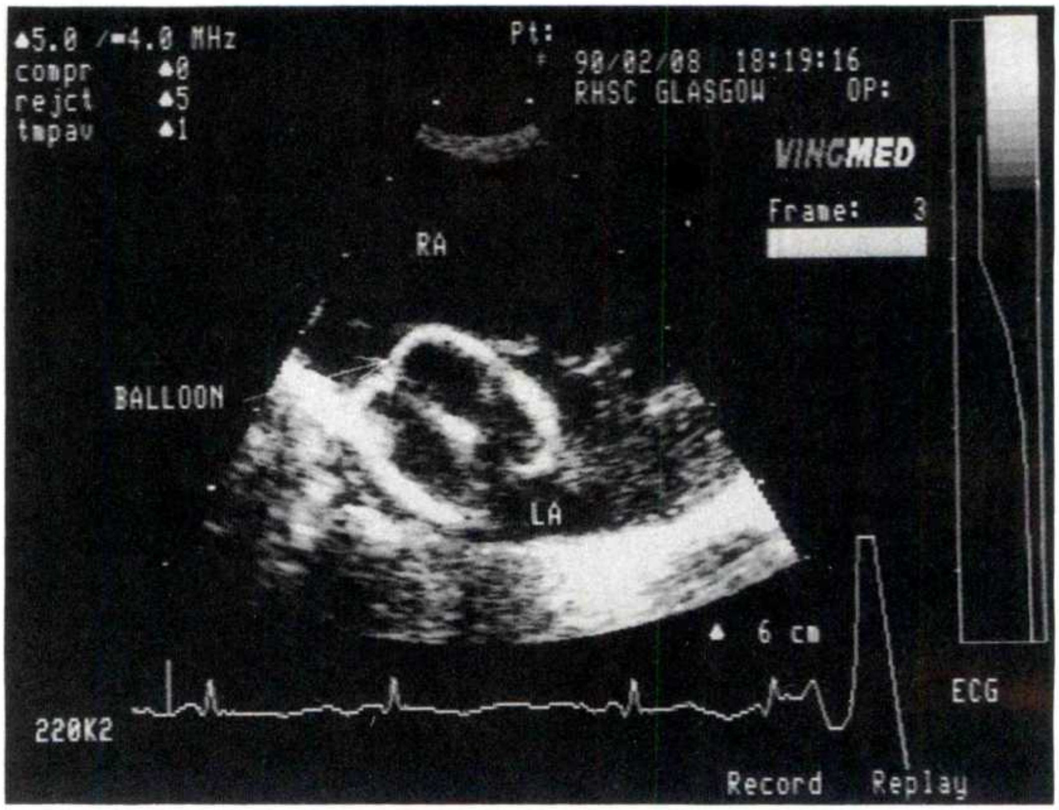

Figure 3 Subcostal view focusing on the interatrial septum. The balloon was inflated in the left atrium and was pulled against the interatrial septum. Note the walls of the inflated balloon.

than two days of age. Four of these patients needed concomitant diagnostic cardiac catheterisation.

We inserted the balloon catheter using a subxiphoid four chamber view as a guiding image. In most infants the catheter passed easily from the right atrium through the patent foramen ovale into the left atrium and only slight manipulation was required. When there was difficulty we used an image obtained by medial angulation and rotation from a subcostal long axis view to guide the passage of the catheter tip through the fossa. This view shows the junction between the inferior vena cava and the right atrium, eustachian valve, atrial septum, and left atrium[7] (fig 2). When the catheter tip was shown to be in the left atrium it was inflated with saline and gently pulled back until it apposed the atrial septum (fig 3) and then it was pulled through into the right atrium. It was inflated with 2–4 ml and pulled back several times until it became easy to pull the catheter through the septal hole and cross sectional and colour Doppler echocardiography showed a good sized hole.

We decided to use echocardiographic imaging for balloon atrial septostomy for 10 months when, because the catheterisation laboratory was being modernised, screening facilities in the hospital were not adequate. We performed the procedure in the ward side room, but later we returned to the catheterisation laboratory because nursing staff and ultrasound and other equipment used in the procedure were available. In addition, in two very ill neonates the procedure was performed in the neonatal intensive care unit.

Results

We used echocardiographic imaging control for septostomy in all patients, including the four who had diagnostic catheterisation. The images were adequate for the procedure in all; none needed fluoroscopy to guide the passage of the catheter through the septum. In all patients the size of the atrial septal defect we created (seen on echocardiographic image or by colour flow mapping) showed that the procedure was successful.

We only attempted to catheterise the umbilical vein in the 37 infants who were <48 hours old. We were unsuccessful in 10: three of the 18 <24 hours old and seven of the 19 aged between 24 and 48 hours of age. Catheterisation or attempted catheterisation of the umbilical vein did not cause any recognisable complications. Two infants died: the first had atrial septostomy by femoral cut down on the eighth day and died the next day of disseminated intravascular coagulation, while the other underwent septostomy through the umbilical vein when he was eight hours old and died from necrotising enterocolitis which developed when he was eight days old.

Discussion

Echocardiography rather than cardiac catheterisation is now used to investigate many aspects of congenital cardiac defects. Defects can be imaged by echocardiography and their severity and haemodynamic importance assessed by Doppler ultrasonography. In many cases surgical intervention can be reliably based on such studies.[8 9]

Interatrial balloon septostomy is a lifesaving palliative technique in patients with transposition of the great arteries and allied conditions. Previously the procedure was performed under fluoroscopic control with the balloon catheter being manipulated in relation to anatomical landmarks on the fluoroscopic image rather than actual visualisation of the interatrial septum and related intracardiac structures such as the atrioventricular valves. With this imaging technique there is the risk that balloon inflation will damage the atrioventricular valves if a balloon thought to be in the left atrium is really in a ventricle.[5]

The intracardiac anatomy is more clearly and precisely displayed when the procedure is undertaken under cross sectional echocardiographic imaging control. In addition, the defect created by the balloon can be seen and accurately measured, a procedure that is virtually impossible with catheterisation and angiography. This approach is helpful in patients in whom the position of the heart is abnormal and it is difficult to see the relative positions of the atrial septum and atrioventricular valves by *x* ray screening. Our findings in this series of 63 patients who underwent balloon atrial septostomy over a period of six years showed that cross sectional echocardiographic imaging was a reliable guide for manipulation of the balloon catheter. Where there is any difficulty in passing the catheter through the atrial septum the modified subcostal view[7] should be used.

We believe that when balloon atrial septostomy is performed under the control of cross sectional echocardiographic imaging the procedure is safer, less time consuming, and avoids exposing the patient and operator to radiation. With this imaging technique the procedure can also be performed at the bedside, in the intensive care unit, or other places where fluoroscopy is not available. It does need the cooperation of two trained operators, one to perform the procedure and the other to obtain the echocardiographic image. Because most centres that treat congenital heart defects now have a good echocardiographic service, it will not be difficult to perform such procedures under the control of ultrasound image.

Most infants requiring atrial septostomy are seen in the first two days of life when the ductus venosus is potentially patent and may be used to perform the septostomy. The technique is simple and quick and can be readily performed in cramped conditions such as in an incubator in an intensive care unit. It has also been stated that "this approach saves a vein".[10] But we failed to pass the catheter in 25% of infants; so is it appropriate to use this approach first rather than the femoral one? Ten years ago the risk of venous thrombosis from percutaneous catheterisation was 16% in infants under six months.[11] Though the real risk now is likely to be lower it cannot be disregarded. As far as we are aware no patient in our series developed such a complication, and in view of this and the small study groups we cannot be certain which approach has fewer complications. In view of the simplicity and safety of using the umbilical route our present policy in those under 48 hours initially is to clean both the umbilicus and the groin; if the catheter does not pass easily through the ductus venosus we then immediately attempt the percutaneous approach through the groin.

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Atrial natriuretic peptide, aldosterone, and plasma renin activity in peripartum heart failure

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Abstract

Plasma concentrations of atrial natriuretic peptide and aldosterone and plasma renin activity were measured in patients with peripartum heart failure and in age matched healthy women post partum. Both groups had carried out traditional postpartum practices of salt consumption and body heating. Plasma concentrations (mean (SEM)) of atrial natriuretic peptide were significantly higher in the seven patients with peripartum heart failure (146·9 (24·3) pg/ml) than in the seven controls (4·4 (0·8) pg/ml). Both plasma aldosterone and plasma renin activity were suppressed in the patients with peripartum heart failure. After treatment for the heart failure plasma atrial natriuretic peptide fell considerably and there were associated increases in plasma aldosterone and plasma renin activity.

The high plasma concentrations of atrial natriuretic peptide may have been a compensatory response to salt and water retention as well as to the heart failure. These high concentrations could also, in part, have suppressed the release of aldosterone and renin in an attempt to correct for volume overload.

Women in and around Zaria in northern Nigeria who develop peripartum heart failure have customarily eaten large quantities of lake salt (Kanwa) and water in the early postpartum period.[1] They are also likely to have performed the ritual of body heating. Both of these practices can increase blood volume and have been associated with high output cardiac failure.[2] These women have no evidence of underlying cardiac or renal disease. Besides the volume expansion, the pressure load of postpartum hypertension may also contribute to the cardiac damage in susceptible individuals. So far the role of the kidney's ability in handling the salt load in peripartum heart failure has not been determined. Several factors are important in the control of renal sodium excretion, in particular the renin-angiotensin-aldosterone system and the newly discovered atrial natriuretic peptides. Little is known about these hormonal determinants in peripartum heart failure. In the present study we measured circulating concentrations of atrial natriuretic peptide, and aldosterone and renin activity in women before and after treatment for peripartum heart failure.

Patients and methods

We studied seven patients (mean age 28; range 21–30 years) with peripartum heart failure. All the patients and controls had carried out the postpartum rituals of body heating. In addition to the estimated daily salt intake of approximately 10 g, all but one patient (case 6) had ingested large quantities of Kanwa, a lake salt. The traditional dose of Kanwa is approximately 30 g/day. This has been estimated to contain 450 mmol of sodium. Kanwa is taken in pap with large amounts of water daily for 40 days or more. The patients were admitted to hospital and their symptoms and signs were recorded. Particular attention was paid to the examination of the cardiovascular system. Blood pressure, pulse, jugular venous pressure, and the precordium were carefully examined. The measurement of jugular venous pressure was used as an indication of central venous pressure. It was measured with the patients semi-sitting at an angle of 30 or 45° with the head turned to the left. The patients were weighed and before treatment routine investigations (chest *x* ray, electrocardiogram, full blood count, urea and electrolytes, serum proteins, urine analysis, and spot urine sodium) were performed. Treatment was started before a 24 h urine sample was collected for the measurement of sodium. Atrial natriuretic peptide (α ANP), aldosterone, and plasma renin activity were measured before treatment and up to seven days after treatment with digoxin, frusemide, and salt restriction. Except for chest *x* rays, the controls also had similar routine investigations and hormone assays.

BLOOD COLLECTION

Venous blood was collected at noon with the woman in the semi-sitting (cardiac) position. The samples were collected into EDTA tubes to measure plasma renin activity; in heparin tubes for aldosterone, and into EDTA tubes plus 15 μl of trasylol solution (5000 KIU/ml; Bayer, Aprotinin) to measure atrial natriuretic peptide. Similar methods were used to analyse blood samples collected after treatment. The blood samples were immediately centrifuged at 4°C and the plasma was stored in clear plastic tubes at −20°C. Plasma samples for renin were preserved in EDTA tubes; those for aldosterone and atrial natriuretic peptide were placed in clear plastic tubes. All samples for hormone measurements were stored at −20°C until they were transported, in the frozen state, to London, where plasma atrial natriuretic peptide, aldosterone, and plasma

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renin activity were measured by radioimmunoassay as described elsewhere.[3]

We used paired or unpaired tests as appropriate for group comparisons. Non-parametric tests were used for urinary sodium and plasma hormone measurements because of considerable differences in sample variances and also because of uncertainty about the form of the distribution for these measurements in the patient group. A p value of < 0·05 was regarded as statistically significant. Results are given as means (SEM).

Results

All controls had normal physical findings, were normotensive, and had normal cardiograms. All the patients with peripartum heart failure were in gross congestive heart failure (class IV, New York Heart Association criteria). Tables 1 and 2 summarise the clinical data. The patient group had slightly raised blood pressure on admission (table 1). This was transient and not consistent with systemic hypertension. Fundoscopic findings in these patients were also normal. In both the patients and controls a full blood count, urine analysis, urea, electrolytes, and serum proteins were all within the normal range. The patients had cardiomegaly on chest *x* ray and the electrocardiogram showed sinus tachycardia and non-specific ST changes. The patients responded promptly to treatment with an average weight loss of 12 (0·8) kg (admission weight 58 (1·7), discharge weight 46 (1·1) kg) and the disappearance of peripheral oedema. Dyspnoea and other symptoms subsided as the jugular venous pressure fell to normal, implying a reduction in the extracellular fluid volume and in pulmonary venous congestion.

Table 1 Clinical data (mean (SEM)) on patients with peripartum heart failure and on healthy puerperal women

Variable	*Controls (n=7)*	*Heart failure (n=7)*	*p value*
Age (yr)	28 (1·5)	28 (1·5)	NS
Last delivery (mnth)	3 (0·7)	3 (0·7)	NS
Parity	5 (0·4)	6 (0·7)	NS
Duration of symptoms (mnth)	—	1·4 (0·4)	—
Systolic blood pressure (mm Hg)	120 (3·8)	140 (9·8)	NS
Diastolic blood pressure (mm Hg)	86 (3·0)	107 (4·5)	< 0·01
Heart rate (beats/min)	85 (4·1)	108 (4·5)	< 0·01
JVP (cm)	—	7 (0·7)	—

JVP, jugular venous pressure.

Table 2 Laboratory data (mean (SEM)) on controls and women with peripartum heart failure

	Controls (n=7)	*Heart failure (n=7)*	*p value*
Packed cell volume (%)	40 (1·9)	38 (1·9)	NS
Spot urinary sodium* (mmol/l)	188 (18·5)	89 (1·5)	< 0·05
Serum albumin (g/l)	43 (1·9)	37 (1·5)	NS
Cardiothoracic ratio	—	0·64 (0·03)	—

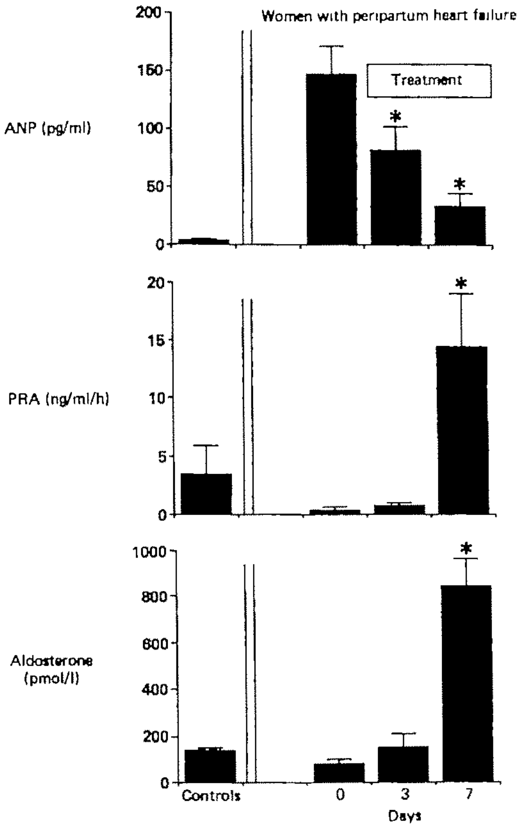
*Treatment started before the 24 hour urine collection was completed

Table 3 Plasma atrial natriuretic peptide, aldosterone, and plasma renin activity in healthy puerperal women and in patients with peripartum heart failure (before treatment)

	Controls (n=7)	*Heart failure (n=7)*	*p value**
Plasma ANP (pg/ml)	4·4 (0·8)	146·9 (24·3)	< 0·01
Plasma aldosterone (pmol/l)	139·0 (15·1)	85·6 (13·7)	< 0·05
PRA (ng/ml/h)	3·4 (2·4)	0·43 (0·24)	NS

*Non-parametric unpaired tests
ANP, atrial natriuretic peptide; PRA, plasma renin activity.

Table 3 shows the plasma concentrations of atrial natriuretic peptide, aldosterone, and renin before treatment in the patients with peripartum cardiac failure and the controls. Plasma concentrations of atrial natriuretic peptide were significantly higher (146·9 (24·3) pg/ml) in the women with peripartum heart failure than in the controls (4·4 (0·8) pg/ml). After treatment for the heart failure plasma atrial natriuretic peptide fell considerably (figure). Before treatment plasma aldosterone in the patients was significantly lower than in the controls (table 3), as was plasma renin activity but not significantly (table 3). In the controls, plasma renin activity ranged from 0·12 to 3·56 ng/ml/h, but one woman had a much higher value (17·93 ng/ml/h). There was no apparent reason for this. After treatment for heart failure both plasma aldosterone and plasma renin activity increased significantly in the women.



Plasma concentrations of atrial natriuretic peptide (ANP), aldosterone, and plasma renin activity (PRA) in seven healthy women post partum and in seven patients with postpartum heart failure before (day 0) and after three and seven days of treatment (mean (SEM));
**p < 0·05 v basal concentrations (day 0)*

Discussion

The exact cause of peripartum heart failure is yet to be identified. It occurs throughout the world, but is most common in the tropics and the tropical parts of temperate countries where hot and humid climatic conditions prevail.[4–6] The high incidence in and around the northern Nigerian city of Zaria, especially during the hot and humid period of the year, has been attributed in part to the postpartum practice of salt loading and body heating in hot and humid rooms.[2] Not all of the women who carry out these practices develop peripartum heart failure, however. It is possible that renal handling of salt is different in those who develop peripartum heart failure. Urinary sodium in spot samples before treatment in the patients with peripartum heart failure were significantly lower than those in the controls (table 2); this suggests sodium and water retention. This resultant salt and water retention could cause a high output cardiac failure. But very little is known about the associated hormonal responses. In the present study we measured plasma concentrations of atrial natriuretic peptide, aldosterone, and renin in the women who developed peripartum heart failure and those who did not have heart failure after the postpartum rituals. Previous studies have shown that plasma concentrations of atrial natriuretic peptide increased in healthy individuals during increased sodium intake[3] and much increased concentrations were reported in patients with overt heart failure.[7 8] In patients with heart failure, the high concentrations of atrial natriuretic peptide before treatment may, therefore, be a response to both the heart failure and to sodium retention; after correction of the heart failure atrial natriuretic peptide concentrations usually return towards normal.[9] In the patients with peripartum heart failure in the present study atrial natriuretic peptide was considerably reduced after treatment (figure). It would have been interesting to measure atrial natriuretic peptide during salt loading and heating, but this was impracticable because at this stage patients stayed at home.

Plasma concentrations of atrial natriuretic peptide in patients were extremely high (in excess of 100 pg/ml) before treatment but two of the seven patients had plasma concentrations of atrial natriuretic peptide below 100 pg/ml. One of these (case 6: plasma atrial natriuretic peptide 59·2 pg/ml) had heated her body but not taken an extra salt load. The intense vasodilatation caused by lying on a heated bed in a hot and humid room, and taking very hot baths twice a day for 40 days may have increased her blood volume enough to induce heart failure.

Before treatment in the patients with peripartum heart failure plasma aldosterone and plasma renin activity were within the normal range but were slightly lower than in the controls (table 3). Treatment reduced the plasma concentration of atrial natriuretic peptide and increased plasma aldosterone and plasma renin activity (figure). These changes most probably reflect the associated reduction in the extracellular fluid volume. Atrial natriuretic peptide may be one of the many factors that are important in the control of renin release.[8] Before treatment atrial natriuretic peptide may have been sufficiently raised to contribute to the observed suppression of renin and aldosterone.

In conclusion, patients with peripartum heart failure have raised concentrations of plasma atrial natriuretic peptide and suppressed concentrations of plasma aldosterone and renin. This accords with heart failure induced by hypervolaemia. The heart failure responded rapidly to treatment and the concentrations of circulating hormones were restored to normal.

We thank Mr M G Buckley, Mrs M Miller, and Dr A L Sugden for the plasma hormone measurements.

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Estimation of Doppler gradients at rest and during exercise in patients with recoarctation of the aorta

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Abstract

In patients with suspected recoarctation of the aorta the estimation of the pressure difference between the arms and legs is an important part of the examination. Because this difference is often augmented when the circulation is stressed by exercise, exercise tests are a useful part of the evaluation. Doppler echocardiography was used to estimate this pressure difference in 16 adult patients in whom simultaneous pressure and Doppler recordings were made both at rest and during exercise. There was a close correlation between the invasive peak instantaneous gradient and the Doppler gradient both at rest and during exercise. There was only a moderate correlation between the invasive peak to peak gradient and the Doppler gradient at rest and during exercise.

Doppler echocardiography is recommended as an easy and accurate method of estimating the peak instantaneous gradient both at rest and during exercise in patients with suspected recoarctation.

In patients operated upon for coarctation of the aorta a good repair results in normal blood pressure and no significant aortic obstruction shown by angiography or magnetic resonance imaging.[1,2] Frequently, however, patients have near normal blood pressure at rest that becomes abnormal during exercise. Whether or not this is always the result of a recoarctation is debatable.[3,4] The increased flow during exercise is expected to unmask an obstruction that may not be evident at rest, and an exercise test is often included in the follow up examination of these patients.[5–7] When patients are studied during exercise, blood pressure is usually recorded immediately after exercise by two blood pressure cuffs at the wrists and ankles and the pressure difference is derived from these measurements.

Though several studies have reported acceptable correlation between gradients measured invasively and by Doppler echocardiography in these patients,[8–10] most have dealt with a mixture of native coarctations and recoarctations[9,11,12] and few have examined pressure differences measured simultaneously by catheterisation and Doppler echocardiography. The inclusion of preobstruction velocities in the calculation of the Doppler gradient by the modified Bernoulli equation is controversial[8,11,12] as is the existence of a significant difference between peak instantaneous gradients and peak to peak gradients in these patients.[8]

Our study examined the use of Doppler echocardiography to estimate gradients at rest and during exercise in an homogeneous group of patients with suspected recoarctation and we performed the invasive and non-invasive measurements simultaneously.

Patients and methods

PATIENTS

We examined a consecutive series of 16 adult patients (three women and 13 men) with a mean age of 30 years (20–55 years). All of them had had resection and end-to-end anastomosis of their lesions.

METHODS

Invasive studies

Pressures were recorded with fluid filled catheters connected to mechanico-electrical transducers interfaced with an ultraviolet strip chart recorder and calibrated against a hydrostatic standard. In eight patients a pull back procedure was performed and the proximal and distal pressure recordings were superimposed with close matching of RR intervals of similar duration. In eight patients a dual catheter technique was used whereby the two catheters were positioned immediately proximal and distal to the recoarctation. The pressures, peak instantaneous gradients, and peak to peak gradients of 3–5 beats were averaged.

Non-invasive studies

The aortic arch was examined with pulsed and continuous wave Doppler on a Vingmed's CFM 700 or 750. The velocities in the ascending aorta were recorded with pulsed Doppler echocardiography and the coarctation jet was recorded with a 2 MHz non-imaging transducer positioned in the suprasternal notch.

The Doppler gradient were calculated according to the simplified Bernoulli equation[13]: $p = 4(V_2^2 - V_1^2)$, where p = gradient (mm Hg), V_1 = ascending aortic velocity (m/s), and V_2 = coarctation jet velocity (m/s). The average values of 3–5 beats were estimated.

All patients were examined at rest and during supine exercise in the catheterisation laboratory. When a satisfactory position of the Doppler probe was achieved Doppler velocities and invasively measured pressures and gradients were recorded simultaneously.

Non-invasively measured (Doppler) gradients (mm Hg) and invasively measured peak instantaneous and peak to peak gradients at rest and during exercise

	Rest			*Exercise*		
Case	*Doppler gradient*	*Invasive peak inst gradient*	*Invasive peak to peak gradient*	*Doppler gradient*	*Invasive peak inst gradient*	*Invasive peak to peak gradient*
1	25	27	16	62	73	64
2	49	40	6	92	92	60
3	19	20	20	44	72	72
4	12	16	0	34	52	48
5	27	44	20	37	48	26
6	12	16	0	27	32	28
7	41	48	42	85	76	68
8	28	34	16	51	66	58
9	12	9	8	20	21	20
10	20	22	8	56	76	14
11	20	32	23	41	64	52
12	9	20	4	22	24	20
13	7	8	2	31	44	36
14	53	46	36	92	88	76
15	18	39	22	37	52	38
16	21	28	12	44	42	20

Interobserver variability

The last 10 patients were examined by two experienced examiners. The differences between the two observers were calculated.

STATISTICAL ANALYSIS

Correlation and linear regression analysis were used to compare non-invasively and invasively measured pressure drops. Agreement between the methods was assessed by the method of Bland and Altman.[14]

Results

The table shows the invasively and non-invasively measured results. The correlation between invasive peak instantaneous gradients and Doppler gradients at rest and during exercise was 0·92 (SD = 9 mm Hg) (n 2 × 16). There was a good agreement between the Doppler estimated gradient and the invasively measured peak instantaneous gradient (fig 1) and between the Doppler gradient and the invasively measured peak to peak gradient (fig 2). Figure 3 shows the pressure recordings of patient 14 at rest and emphasises the difference between peak instantaneous and peak to peak gradients in these patients.

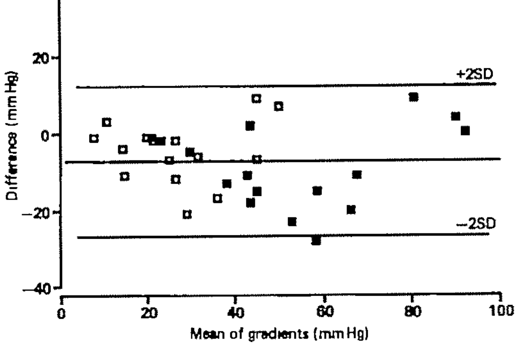

Figure 1 Difference between the Doppler gradient and the invasively measured peak instantaneous gradient plotted against the mean of both methods. Open symbols are results recorded at rest and solid symbols the results during exercise. One open symbol represents the results of two patients.

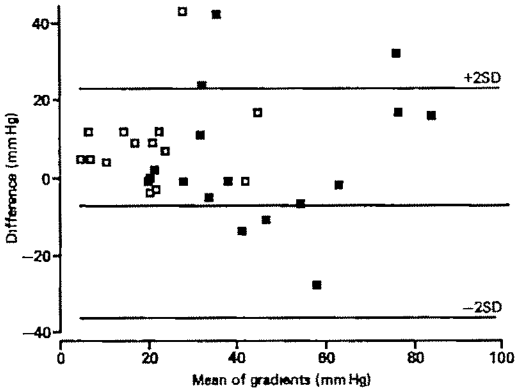

Figure 2 Difference between the Doppler gradient and the invasively measured peak to peak gradient plotted against the mean of both methods. Open symbols are results recorded at rest and solid symbols the results during exercise. One open symbol represents the results of two patients.

The mean difference in calculated gradient between the two observers was 1·3 mm Hg (0–3 mm Hg) at rest and 3·3 mm Hg (1–5 mm Hg) during exercise.

Discussion

We showed that it is possible to estimate the gradient across the coarctation site by Doppler cardiography even during exercise. The method is easy to perform and certainly far more simple than the use of two blood pressure cuffs. It has also the advantage over the cuff method that the gradient is estimated during exercise and not subsequently within a variable time interval. We believe that this is an important point; it will be addressed in a later study. Our results also showed the closest correlations between the Doppler gradients and the invasive peak instantaneous gradients. This finding is expected from findings in patients with aortic stenosis.[15]

There are frequently considerable differences between the Doppler gradient and the invasively measured peak to peak gradient (table). At least three factors will tend to give a Doppler gradient larger than the invasive peak to peak gradient: (*a*) the difference between peak instantaneous and peak to peak gradient as shown in fig 3; (*b*) if the velocities proximal to the obstruction are not subtracted this will magnify the Doppler gradient; and (*c*) the effect of pressure recovery distal to the obstruction[16] will influence the results. A small angle error almost always affects Doppler echocardiography and when this is significant the Doppler technique will underestimate the peak instantaneous gradient. We believe this explains why the Doppler gradient was less than the peak to peak gradient in some of our patients. Our Doppler results showed larger gradients than the invasive peak to peak gradient in most patients.

Simultaneous invasive and non-invasive measurements are important for the comparison of gradients in these patients with varying numbers and sizes of collateral vessels where the relation between flow, gradients, and degree of obstruction is more complicated than when

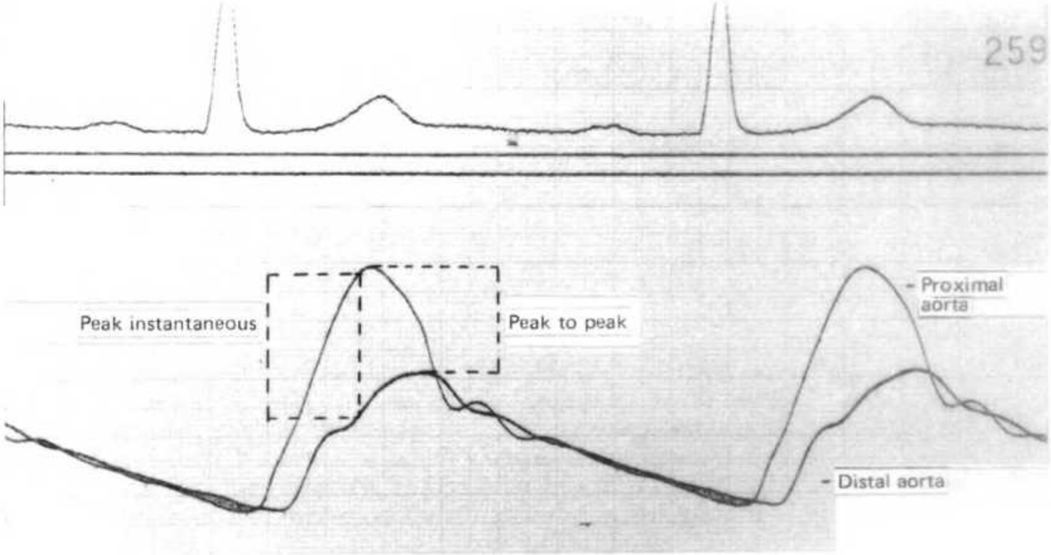

Figure 3 Typical recording of proximal and distal pressures showing the difference between peak instantaneous and peak to peak gradient.

there is a valve lesion. It was not the purpose of this study to determine the clinical implications of the measurd pressure drops and their relation to anatomical obstruction. We found that even during exercise reliable Doppler-derived gradients can be recorded with low interobserver variability.

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Br Heart J 1991;65:158–60

Two cases of left superior vena cava draining directly to a left atrium with a normal coronary sinus

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Abstract
The most common variation in the thoracic systemic venous system is a persistent left superior vena cava draining to a coronary sinus. A rare anomaly is a persistent left superior vena cava connecting directly to the left atrium. In this situation it is believed that the coronary sinus must be absent. This report describes two cases of a persistent left superior vena cava draining to a left atrium with a normal coronary sinus.

The embryological development of systemic and pulmonary veins is complex and subject to considerable variation. The early, symmetrical cardinal veins ultimately give rise to the superior systemic venous channels while the splanchnic plexus of the foregut gives rise to the pulmonary venous channels. Most of the left sided cardinal system disappears, leaving only the coronary sinus to drain the cardiac veins and a remnant known as the ligament of Marshall. Many variations and abnormalities of venous development have been described.[1-3] One variation is the persistence of a left superior vena cava,[4] which usually drains into the coronary sinus. A rare abnormality is the presence of a persistent left superior vena cava draining directly into the left atrium.[5 6] It is often stated that a persistent left superior vena cava draining into the left atrium is associated with an absent coronary sinus. We describe two patients in whom a persistent left superior vena cava draining to the left atrium was associated with a normal coronary sinus.

Case reports

CASE 1

A two year old child with tetralogy of Fallot had cardiac catheterisation before elective surgical repair. His clinical course was unremarkable except for slowly progressive cyanosis. Haemodynamic evaluation during catheterisation showed an unrestrictive ventricular septal defect (right and left ventricular peak pressures 90 mm Hg), infundibular and pulmonary valve stenosis (main pulmonary artery peak pressure 12 mm Hg), and unobstructed left ventricular outflow (right femoral artery peak pressure 110 mm Hg). Oximetry did not show a left to right shunt (mixed venous 71% and main pulmonary artery 69%). There was right to left shunting at both the atrial and ventricular levels (pulmonary vein 96%, left atrium 93%, left ventricle 93%, and femoral artery 86%).

Both catheterisation and angiography showed a persistent left superior vena cava connected to the roof of the left atrium (fig 1). The left superior vena cava ran in front of the left pulmonary artery and was connected to the normal left innominate vein at its junction with the left subclavian vein. There was also a normal right superior vena cava and a patent foramen ovale. The catheter passed anterogradely from the left superior vena cava into the left atrium as well as retrogradely from the left atrium into the left superior vena cava. The catheter also passed from the right atrium into the coronary sinus, which did not communicate with any systemic vein except the cardiac veins (fig 2). The pulmonary veins were connected to the left atrium.

CASE 2

A nine month old infant had a complete atrioventricular canal, pulmonary hypertension, and failed to thrive. He underwent cardiac catheterisation before pulmonary artery banding. At catheterisation the right and left ventricular peak pressures were equal (70 mm Hg). Oxygen saturation data measured by oximetry showed a left to right shunt at the atrial and ventricular levels (mixed venous 63%, right atrium 81%, right ventricle 85%, and main pulmonary artery

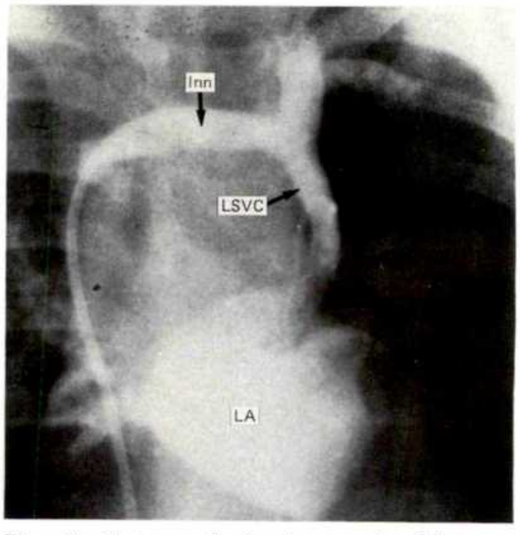

Figure 1 Angiogram showing the connection of the persistent left superior vena cava (LSVC) to the roof of the left atrium (LA). The catheter passed from the right atrium through the right superior vena cava and left innominate vein (Inn) into the left superior vena cava.

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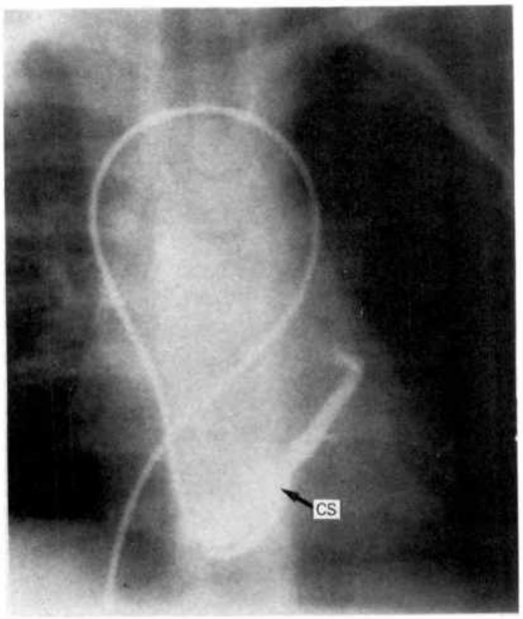

Figure 2 Angiogram showing that the normally formed coronary sinus (CS) is separate from the left superior vena cava (see fig 1). The catheter course is inferior vena cava, right atrium, patent foramen ovale, left atrium, left superior vena cava, innominate vein, right superior vena cava, right atrium, and mouth of the coronary sinus.

85%). Data were not collected to document the degree of right to left shunting.

Angiography and the catheter course showed a persistent left superior vena cava connected to the roof of the left atrium. This vein ran in front of the left pulmonary artery and was connected to the left subclavian vein. There was no bridging left innominate vein. The pulmonary veins entered the left atrium as normal.

The postoperative course was complicated and the patient died 27 days after operation. At necropsy the findings at catheterisation were confirmed: complete atrioventricular canal and a persistent left superior vena cava to the left atrium. In addition, a normal coronary sinus was found with normal connection to the right atrium. This coronary sinus was not connected to any systemic vein other than the cardiac veins.

Discussion

Embryological development of the systemic veins involves the umbilical, vitelline, and cardinal venous systems. The anterior and posterior cardinal veins join to form the right and left common cardinal veins which empty into the sinus horns and then into the primitive atria. Invagination of the sinus horns, which causes both the common cardinal veins to empty into the right atrium, and obliteration of the anterior cardinal vein leaves the normal coronary sinus, with absence of the left superior vena cava, as found in the mature heart.[7] Many variations and abnormalities of this development have been reported. The most common thoracic venous abnormality is the persistent left superior vena cava draining into the coronary sinus as reported in 3–10% of patients with congenital heart disease.[8 9] This variation in isolation results in no haemodynamic compromise. A more uncommon

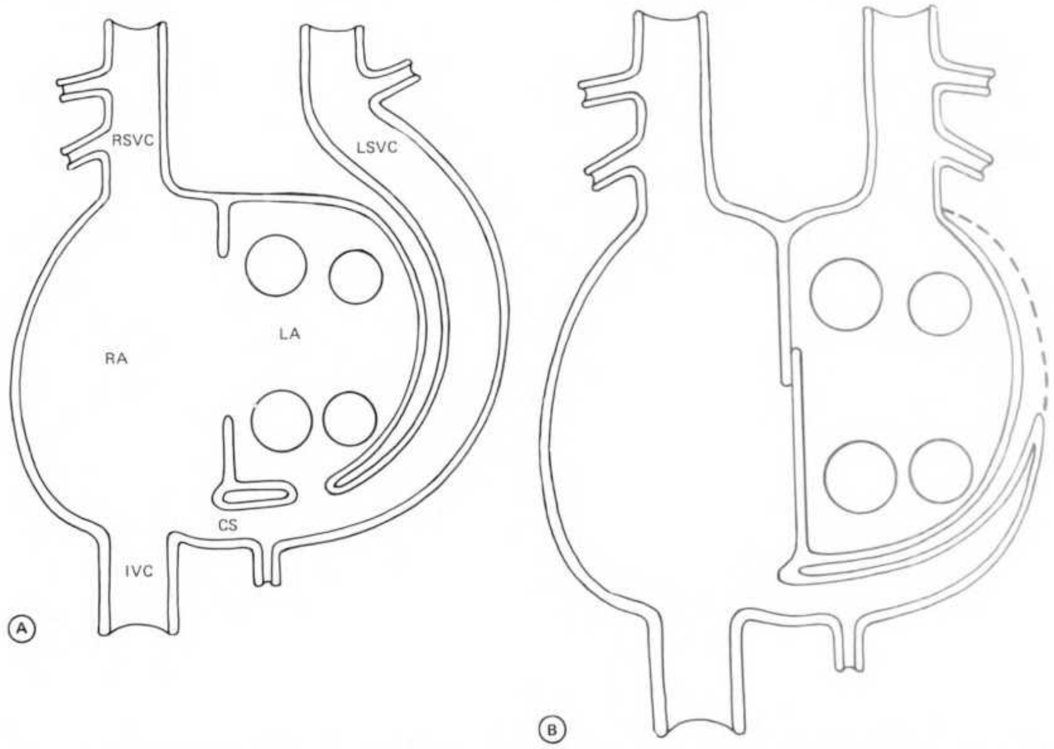

Figure 3 A theory to explain the association between a persistent left superior vena cava (LSVC) to left atrium and a normal coronary sinus. (A) The left superior vena cava retains a communication with the left atrium ("unroofed") while the coronary sinus develops normally. (B) If this communication persists and the left superior vena cava does not regress, then both a left superior vena cava to left atrium and coronary sinus can exist together. LA, left atrium; RA, right atrium; RSVC, right superior vena cava; LSVC, left superior vena cava; IVC, inferior vena cava; CS, coronary sinus. (Adapted from Lucas RV. Anomalous venous connections, pulmonary and systemic. In: Adams FH, Emmanouilides GC, eds. Moss' heart disease in infants, children, and adolescents. 3rd ed. Baltimore: Williams and Wilkins, 1983:483.)

abnormality is the persistence of a left superior vena cava connecting directly to the left atrium. This anomaly was found in about 7·5% of cases of persistent left superior vena cava,[10] and it results in a small right to left shunt. This lesion has little haemodynamic effect, mainly a variable degree of systemic cyanosis.[7]

Various workers believe that the embryological anomaly of the left superior vena cava connecting into the left atrium cannot exist with a normal coronary sinus.[6 7 11] Presumably a left superior vena cava is produced when the left common cardinal vein and the left sinus horn are incorporated into the right atrium during invagination of the sinus horns and the left atrium. Failure of this invagination allows the left superior vena cava to remain connected to the left atrium and makes development of the coronary sinus impossible (fig 3). If this were true then an atrial septal defect of the coronary sinus type should be present in every case. This finding is not present in all reported cases.

Edwards and DuShane described one patient who had a connection to the left atrium, pulmonary veins, and systemic veins via a "levoatriocardinal vein".[1] This patient had mitral atresia with a closed foramen ovale. Presumably in this patient this vein carried pulmonary venous blood away from the left atrium. Lucas *et al* described a similar case of severe left atrial obstruction with a "levoatriocardinal vein" draining pulmonary venous return.[12] Anomalies of pulmonary venous connections often involve veins connecting the common pulmonary confluence with the left innominate vein. These connecting veins have often been termed "vertical veins" and are not considered to be a truly persistent left superior vena cava.[7 13]

Mantini *et al* described anomalies of the coronary sinus, including connection to the left atrium and pulmonary veins.[14] One patient had atresia of the mouth of the coronary sinus with the distal end of the coronary sinus connected to the left atrium in association with a left superior vena cava that was also connected to the left atrium. When a portion of the atrial wall near the mouth of the coronary sinus is missing (coronary sinus atrial septal defect) or when the coronary sinus is "unroofed" there is usually a communication between the coronary sinus and left atrium.

We report two patients with a truly persistent left superior vena cava connected directly to the left atrium in association with a normally formed coronary sinus. These systemic veins were regarded as true left superior venae cavae because they connected to the roof of the left atrium, did not connect to or drain the pulmonary veins, passed in front of the left pulmonary artery and aortic arch, and connected to the left innominate vein or left subclavian vein in this instance without a left innominate vein. "Vertical veins" and "levoatriocardinal veins" do not have these characteristics. In addition, the coronary sinus was clearly seen by either angiography or direct visualisation. Figure 3 shows a theory to explain this association of left superior vena cava with left atrium and normal coronary sinus. A connection between the left cardinal vein and left atrium remains (similar to an unroofed coronary sinus) while the distal coronary sinus develops normally. The left superior vena cava retains this connection to the left atrium but loses its connection to the coronary sinus. There is no obvious reason for the coronary sinus to become involved when the left common cardinal vein retains a connection with the left atrium.

This report shows the association between the rare anomaly of a persistent left superior vena cava to left atrium and a normal coronary sinus. Both patients described had other cardiac malformations requiring catheterisation which showed the additional venous abnormality. We do not know whether this rare association ever occurs without other intracardiac malformations. The haemodynamic results of a small right to left shunt in such a situation are unlikely to be noticeable.

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Br Heart J 1991;**65**:161–2

CASE REPORTS

Aortic-ventricular tunnel in a neonate: diagnosis and management based on cross sectional and colour Doppler ultrasonography

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Abstract

A five day old symptom free neonate was referred for assessment of a to and fro murmur associated with large volume pulses. Cross sectional echocardiography and colour flow mapping confirmed the diagnosis of an aortic-ventricular tunnel with forward flow into the aorta and regurgitant flow into the ventricle through both the tunnel and the dilated aortic valve ring. Surgical correction by patch closure of the aortic end of the tunnel was successfully undertaken two weeks later without any additional investigations. Postoperative echocardiography and colour flow imaging showed no aortic regurgitation and normal left ventricular dimensions and function.

An aortic-ventricular tunnel is a rare congenital malformation that presents with clinical signs of aortic regurgitation and may produce cardiac failure in infancy. There are a few reports of successful diagnosis by cross sectional and Doppler ultrasound and the diagnosis has been based mainly on the demonstration of the tunnel by aortic root angiography.[1-3] It may, however, be difficult to show the intracardiac portion of the tunnel, particularly when there is gross distortion of the left ventricular outflow tract. In addition, angiography is not without risks in the sick neonate. We describe a neonate in whom the diagnosis of an aortic-ventricular tunnel was confirmed by cross sectional echocardiography with Doppler colour flow imaging, and successful surgical repair was undertaken on the basis of these investigations alone.

Case report

A five day old female infant weighing 2·7 kg was referred for the assessment of a to and fro murmur that had been noted at routine examination after an uncomplicated vaginal delivery. At examination she was symptom free but had bounding pulses associated with an ejection systolic and early diastolic murmur grade III that was best heard in the third intercostal space at the left sternal edge. The chest *x* ray showed cardiomegaly (cardiothoracic ratio 0·68) with a widened mediastinal shadow; the electrocardiogram showed left ventricular hypertrophy with non-specific changes in the ST segment and T wave.

ECHOCARDIOGRAPHY

Cross sectional echocardiography showed a dilated left ventricle with concentric hypertrophy but good contractility. In the parasternal long axis view a tunnel could be seen arising from the region of the right aortic sinus and passing between the aortic valve and the outlet portion of the ventricular septum to terminate in the left ventricle (fig 1A). Parasternal short axis scans at the level of the aortic root showed the relation of the tunnel to the right aortic sinus and coronary artery (fig 1B). The aortic valve had three cusps of equal

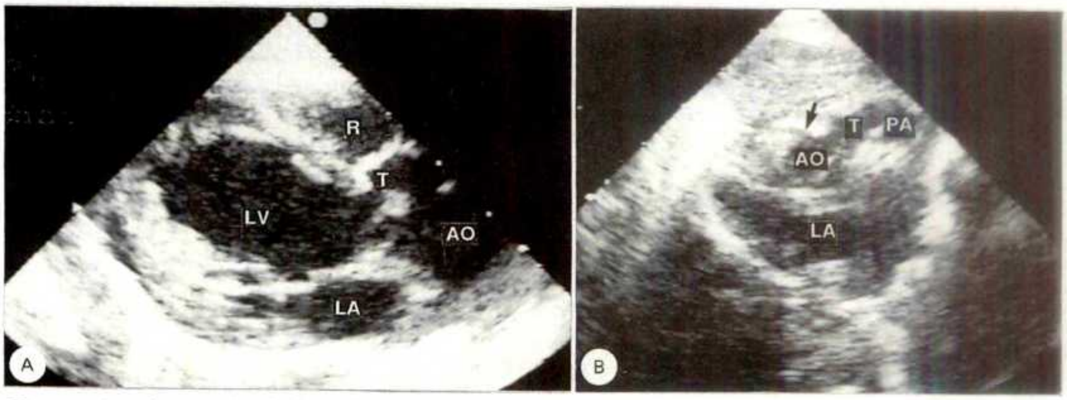

Figure 1(A) Cross sectional echocardiogram in the parasternal long axis view showing the entire extent of the tunnel between the aorta and left ventricle. AO, aorta; LA, left atrium; LV, left ventricle; R, right ventricular outflow tract; T, tunnel. (B) Cross sectional echocardiogram in the parasternal short axis view at the level of the aortic root showing the relation of the tunnel to the right coronary artery (arrow) and coronary sinus. AO, aorta; LA, left atrium; PA, pulmonary artery; T, tunnel.

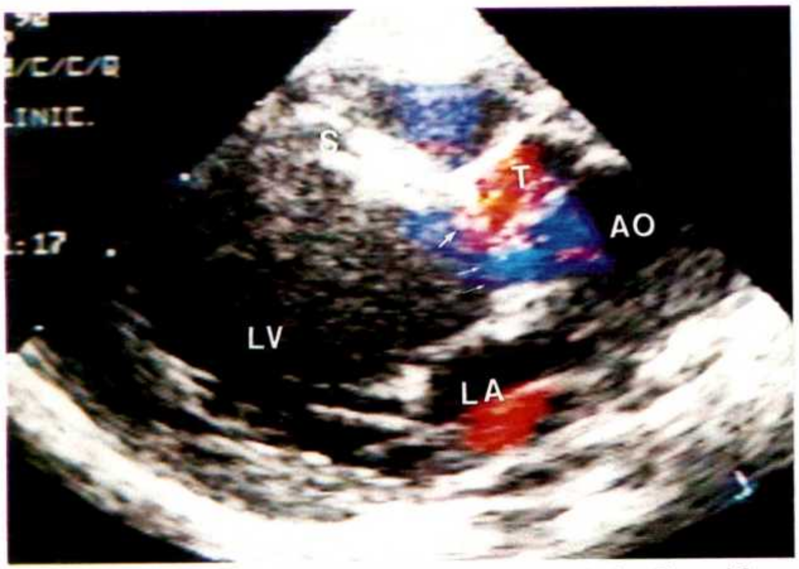

Figure 2 Doppler colour flow imaging in the parasternal long axis view. Forward flow through both the aortic valve (double arrows) and the tunnel (single arrow) are shown in this systolic frame. Regurgitation through both the tunnel and the dilated valve ring was seen in diastole. AO, aorta; LA, left atrium; LV, left ventricle; S, interventricular septum; T, tunnel.

size and seemed to open normally. The origins of both coronary arteries were shown and were normal. Colour flow mapping confirmed unobstructed to and fro flow through the tunnel (fig 2). In addition, there was also central aortic valve regurgitation caused by a dilated aortic valve ring. The patient was initially treated with digoxin and diuretics but at review two weeks later she had signs of heart failure. Repeat echocardiography showed further dilatation of the left ventricle with impaired function. Urgent surgical repair was therefore undertaken.

At operation the aortic valve was between 8 and 9 mm in diameter. The aortic end of the tunnel was apparent as a dilatation of 5 mm in diameter in the aortic root to the left of the origin of the right coronary artery. The aortic end of the tunnel was closed with a small Gore-tex patch and tension or distortion of the sinus and aortic valve leaflets was avoided. The postoperative course was uncomplicated and the patient was discharged 10 days after operation. On examination at discharge she had normal volume pulses. A soft ejection systolic murmur could be heard along the left sternal edge. There were no diastolic murmurs, and echocardiography confirmed good left ventricular function. Colour flow imaging showed that there was no aortic regurgitation either through the tunnel or the aortic valve. The blind ended intraventricular portion of the tunnel could be seen to fill in systole and collapse in diastole. Normal peak systolic velocities of flow across the aortic valve were recorded with pulsed wave Doppler.

Two months after operation the clinical and echocardiographic findings were unchanged. The electrocardiogram showed regression of the left ventricular voltages associated with a decrease in the cardiothoracic ratio (0·6) on the chest *x* ray. All treatment for heart failure had been stopped.

Discussion

A tunnel between the aorta and left ventricle is a rare malformation in which a communication between the aorta and the left ventricle bypasses the aortic valve. The lesion typically presents with a to and fro murmur and has to be considered whenever isolated aortic regurgitation is suspected in infancy. The natural course depends upon the degree of aortic regurgitation. In general, there is progressive heart failure and the patient dies if surgical intervention is not undertaken,[4] though the occasional patient has survived to adult life apparently free of symptoms. While the immediate results of surgery have been good, long term follow up of patients treated surgically seems to show that a considerable proportion of patients have persistent aortic valve regurgitation after closure of the tunnel and require further surgery.[5] Most patients with persistent aortic valve regurgitation, however, are older at operation and by then there is considerable dilatation of the aortic root and distortion of the aortic valve apparatus caused both by left ventricular dilatation and longstanding high velocity turbulent flow through the tunnel. In contrast, in the only report on long term follow up after operation in infancy, no aortic regurgitation was seen five years after operation, despite persistence of the blind ended intramural portion of the tunnel.[6] Early repair of the lesion is therefore indicated, even when there are no symptoms. The onset of cardiac failure two weeks after initial diagnosis in this previously well infant shows the unpredictable clinical course.

Colour Doppler flow mapping was useful in identifying and distinguishing regurgitation through both the tunnel and the aortic valve, which angiography often fails to do. The combination of colour Doppler flow mapping and high resolution cross sectional imaging should reliably identify most coexisting defects. This technique is also useful for serial non-invasive follow up assessment of left ventricular and aortic valve function. Such studies of a larger series of patients operated on in infancy are needed to determine whether early operation reduces the frequency of aortic valve regurgitation and resultant morbidity.

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Br Heart J 1991;65:163-5

Impending paradoxical embolism: a rare but important diagnosis

M E Speechly-Dick, S J Middleton, R A Foale

Abstract

A man aged 50 presented with a history of a cerebrovascular accident and arterial embolism at two discrete peripheral sites. Echocardiography showed thrombus trapped in an interatrial site and impending paradoxical embolism was diagnosed. Treatment with heparin was started and the potentially embolic intracardiac material was removed at open heart surgery. The patient was treated with warfarin and made a good recovery. This is only the third case report of impending paradoxical embolism diagnosed in life.

Impending paradoxical embolism is rarely diagnosed in life. Two previous cases have been reported; one was diagnosed with transoesophageal echocardiography and the other by conventional cross sectional contrast echocardiography.[1 2] In both cases the impending embolus was trapped in an interatrial site. Criteria for the anatomical diagnosis were established by Johnson before the introduction of echocardiography.[3] According to these criteria the diagnosis should be made only when embolic material can be shown at angiography straddling the site of the left to right shunt about the time of systemic embolisation. Johnson, however, also described how a paradoxical embolism could be provisionally diagnosed in the absence of either embolic material straddling the atrial septum or a thrombus seen in the venous system, or the demonstration of an abnormal communication between the right and left circulations. These criteria were clinical, angiographic, or pathological evidence of systemic embolism together with evidence of a favourable pressure gradient for blood flow from the right to left side of the heart. We report a third case of impending paradoxical embolism which illustrates both the variety of the condition and also how easily the diagnosis of paradoxical embolism can be overlooked despite an apparently adequate investigation.

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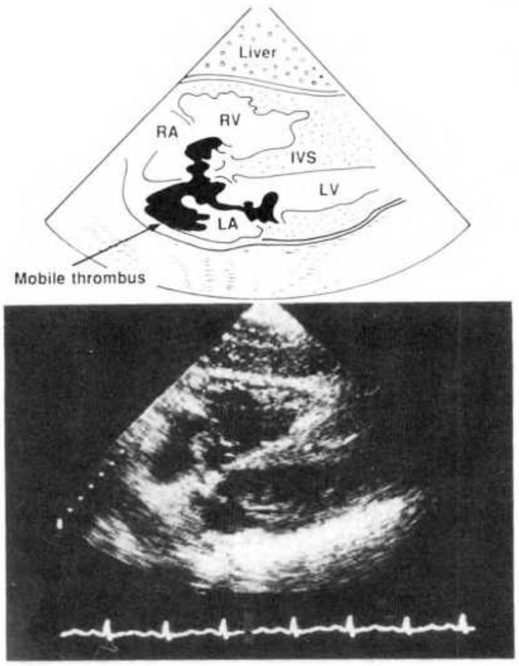
Case report

A 50 year old West Indian man was transferred from another hospital where he had been an inpatient for one month after his emergency admission with a cerebrovascular accident. Five days before this admission he had presented to an accident and emergency department with a pulseless, cold left foot; this resolved within 24 hours. The day before his admission he had been seen again at a second accident and emergency department with amaurosis fugax and an outpatient appointment had been arranged. He was eventually admitted as an emergency after the development of what was on clinical grounds a large right cerebral infarct in the territory of the middle cerebral artery, with midline shift and oedema confirmed on the computed tomogram.

This patient's past medical history included longstanding pulmonary sarcoid, hypertension, and left ventricular failure. He had smoked heavily until six years before admission. At admission he was taking captopril (25 mg), frumil (amiloride hydrochloride (5 mg) and frusemide (40 mg)), and enteric coated prednisolone (20 mg) once a day and was using salbutamol and ipratropium nebulisers. There was nothing else of note in his history. Echocardiography was performed two days after admission to exclude a cardiac source of his multiple emboli. This echocardiogram was technically unsatisfactory but was reported to be normal except for the possibility of a small abnormality in the atrial septum, which was of uncertain clinical importance. His clinical course remained uneventful and he was treated with a reducing dose of steroids, subcutaneous heparin, and physiotherapy.

Echocardiography was repeated after four weeks and on this occasion showed an intracardiac mass extending from the left to the right atrium via an atrial septal defect. He was then transferred to our hospital for further assessment. Repeat echocardiography confirmed the presence of the intracardiac masses (figure). The appearance of the mass was consistent with thrombus. It clearly straddled the interatrial septum and was highly mobile within both atria; during diastole it prolapsed through both atrioventricular valves. Heparin treatment was started and the next day the patient underwent open heart surgery with cardiopulmonary bypass. Organised thrombi were removed from both atria and the stretched foramen ovale was closed. These intracardiac masses were confirmed to be thrombi on histological examination and were sterile on culture. Because they looked like venous casts, it seemed likely that they had originated in the deep veins of the legs. The patient made an uneventful postoperative recovery. He continues to be treated with warfarin, which was started postoperatively, and with rehabilitation his mobility and independence are improving.



A subcostal four chamber echocardiogram showing a mobile thrombus straddling the interatrial septum and lying within left and right atria. IVS, interventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Discussion

Paradoxical embolism is a well recognised complication of a right to left communication which is usually diagnosed at necropsy. We know of 37 reported cases[1,2,4-6] of which only two were diagnosed in life. A deep venous thrombosis can give rise to pulmonary emboli which cause an increase in right atrial pressure. If there is a primitive communication between the atria, for example a frank atrial septal defect or incompletely fused fossa ovalis, the rise in right atrial pressure allows thrombus to cross into the systemic circulation and may give rise to paradoxical arterial embolisation.

A review of the features surrounding the event of paradoxical embolism showed that 60% of paradoxical emboli occur at the onset of symptoms of pulmonary embolism, probably because the resultant increase in right atrial pressure opens the unfused fossa ovalis and therefore the right to left shunt.[4] Fifteen per cent of paradoxical emboli seem to occur during a manoeuvre that raises right heart pressure and 5% occur against a background of chronically raised right heart pressure.[2,4,7] A necropsy review by Loscalzo of 30 patients with paradoxical embolism showed that most had a patent foramen ovale, a relatively common anatomical abnormality; in only a few was the right to left shunt caused by an atrial septal defect.[2] This reported incidence of a patent foramen ovale was confirmed by other reports.[4,7] About a third of Loscalzo's patients had two or more defined embolic sites as did our patient; in 37% of patients these were primarily cerebral.

We diagnosed impending paradoxical embolism in our patient on the basis of Johnson's original criteria but with conventional echocardiography as the imaging method. Subtle interatrial connections are better visualised by transoesophageal echocardiography.[2,8] None the less, the potential for a right to left shunt can be demonstrated by contrast echocardiography and manoeuvres that raise right sided pressures (such as the Valsalva manoeuvre).

Patients with systemic emboli and a clot in the right atrium shown by conventional echocardiography are at a high risk of paradoxical embolism developing and require urgent treatment. In our patient echocardiography showed a thrombus straddling an interatrial communication and review of the echocardiographic data suggested that this thrombus was present at the time of first echocardiographic examination and that it gave rise to the patient's systemic emboli.

In two groups of patients the likelihood of paradoxical emboli is high: (*a*) those who have venous thrombosis or pulmonary embolism associated with systemic arterial embolisation; and (*b*) those with arterial embolisation with no obvious evidence of a left sided cardiac source. Patients in either of these groups should be investigated with cross sectional contrast echocardiography; if this does not detect a right to left shunt, transoesophageal contrast echocardiography should be used. The aetiology of the embolus in embolic stroke is undetermined in approximately 36% of patients[9]; a considerable proportion of these may be a consequence of paradoxical embolisation.

When a paradoxical embolism is diagnosed, measures should be taken to prevent a recurrence. Treatment has included anticoagulation[1,2,4,10] to prevent the formation of further venous emboli, interruption of the inferior vena cava,[11] and surgery to close the right to left shunt and remove intracardiac thrombus.[1,2] In our patient we elected to remove the potentially embolic intracardiac material at open heart surgery on cardiopulmonary bypass and to close the patent foramen ovale. Obviously we cannot compare these treatments but a review of published reports suggests the following treatment strategies. All patients should be anticoagulated unless this is contraindicated—for example, by a haemorrhagic cerebrovascular accident. The optimum length of time of anticoagulation is not known but should be indefinite if there is an underlying untreated cause of venous thrombosis. Peripheral emboli should be treated by embolectomy or thrombolysis as indicated. Ligation of the vena cava cannot be recommended because of considerable mortality and high recurrence rates.[12] The cardiac defect is most commonly a patent foramen ovale, which should remain closed when the right atrial and other right heart pressures are normal; under these circumstances surgical correction is not indicated for paradoxical embolism.

Paradoxical embolism may be more common than is currently thought.[11] The diagnosis should be considered whenever arterial embolisation has no obvious cause. Echocardiography should be performed to determine whether a right to left shunt is present, and venous thrombosis should be excluded. Correct diagnosis allows prompt treatment to be given and may prevent further catastrophic emboli.

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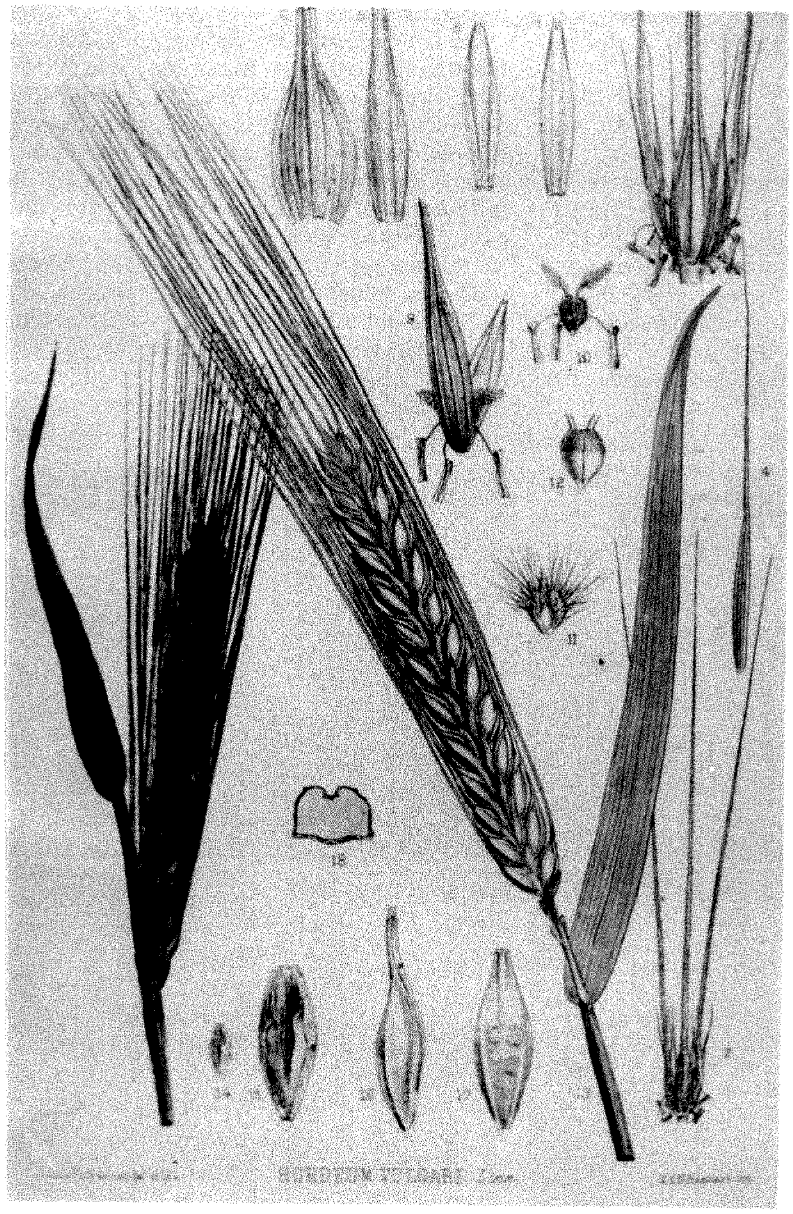
PLANTS IN CARDIOLOGY



Hordeum vulgare L. Bentley R, Trimen H. *Medicinal plants*. Vol 4. London: Churchill, 1880:293.

Lignocaine

In 1932 Professor Hans von Euler pioneered a new concept when he sought chemical differences between genetically different types of plant. For his first study he chose a chlorophyll defective mutant of barley, *Hordeum vulgare*, and isolated a compound $C_{11}H_{14}N_2$ which was not present in normal barley, or in other green plants that he tested. He called the compound gramine after the plant's family Gramineae and he thought that it was 2-(dimethylaminomethyl)-indole. But when his assistant Holger Erdtman synthesised this compound in 1935 it proved to be isogramine not gramine, which is 3-(dimethylaminomethyl)-indole. When Erdtman tasted the isogramine he found that it anaesthetised his tongue which gramine did not. But isogramine was too irritant to use as a local anaesthetic and although Erdtman and Nils Lofgren with the support of Astra synthesised several analogues they also could not be used clinically.

The work then stopped for some years but Lofgren later resumed the project, again with Astra's support and in 1943 he produced Xylocaine, which after extensive testing was marketed in 1948. Its generic names are lignocaine and lidocaine.

Gramine was, however, also isolated by Russian workers in 1935 from the great reed *Arundo donax* L. This plant claimed attention because camels refused to eat it because of its bitter taste.

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Electrocardiographic findings in a patient with pure septal infarction

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Abstract

The electrocardiogram in a 65 year old man in whom pure septal infarction had been produced by occlusion of the septal branch during percutaneous transluminal coronary angioplasty showed that this had led to the disappearance of septal Q waves and reciprocal ST segment depression in the inferior leads.

There are two published reports of pure septal infarction but neither gives detailed electrocardiographic data.[1 2] We report on the electrocardiographic changes produced by pure septal infarction in a patient whose large septal branch was accidentally occluded during percutaneous transluminal coronary angioplasty.

Case report

A 65 year old man was admitted to our hospital with exercise induced angina. On admission, physical examination, chest radiograph, and electrocardiograms (both at rest and after a Master two-step test) were normal. An echocardiogram showed normal wall motion in the interventricular septum and slightly reduced motion in the left ventricular anterolateral wall.

Coronary angiography showed no significant narrowing of the left circumflex or right coronary arteries. The left anterior descending coronary artery (fig 1A and 1B) gave off well developed first septal and diagonal branches at the same level. The left anterior descending artery was completely obstructed just distal to the origins of the first septal and diagonal branches. Collateral vessels from the right coronary artery filled the peripheral left anterior descending artery distal to the occluded site. There were also stenoses (diameter of the lumen reduced by 90%) of both the left anterior descending artery just proximal to the origins of the first septal branch and the proximal portion of the diagonal branch.

On the basis of these findings, percutaneous transluminal coronary angioplasty was performed on the stenoses of the left anterior descending artery and the diagonal branch. Because the two target sites were close to each other we expected that one inflation of the balloon would dilate both lesions. Slight chest pain persisted after deflation of the balloon. Repeat angiography (fig 1C and 1D) showed sufficient dilatation of the target lesions, but complete obstruction of the proximal portion of the septal branch. The electrocardiogram recorded immediately after percutaneous transluminal coronary angioplasty showed

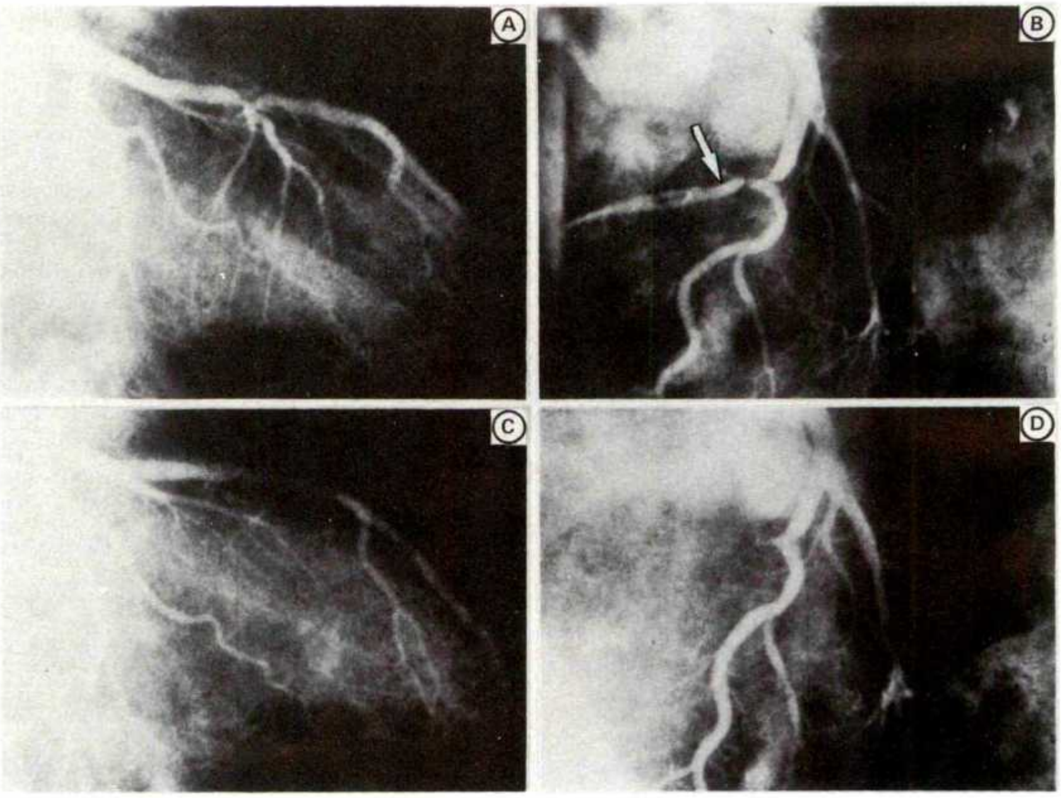

Figure 1 Coronary angiograms (A and B) of the left coronary artery before percutaneous transluminal coronary angioplasty, showing the first septal branch (arrow on B) originating from the left anterior descending coronary artery. Coronary angiograms of the left coronary artery after angioplasty (C and D) showing successful dilatation of the stenotic lesions in the left anterior descending coronary artery and diagonal branch and accidental occlusion of the first septal branch. A and C, right anterior oblique view; B and D, left superior oblique view.

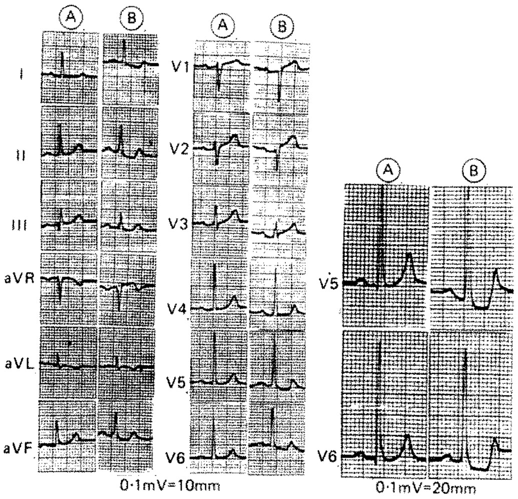

Figure 2
Electrocardiograms before (A) and after angioplasty (B).

that septal Q waves recorded in leads I, V5, and V6 immediately before percutaneous transluminal coronary angioplasty had disappeared (fig 2). There was also slight ST segment elevation and absence or reduction of initial R waves in leads V1–V3, with ST segment depression in leads I, II, III, aVF, V5, and V6. Chest pain disappeared after two hours and the maximum serum concentration of creatine kinase was 937 IU/l. Echocardiography after percutaneous transluminal coronary angioplasty showed akinesis of the anterior interventricular septum. Thallium-201 myocardial imaging after percutaneous transluminal coronary angioplasty showed a perfusion defect in the anterior interventricular septum.

Discussion

Disappearance of initial R waves in leads V1 and V2 have been reported in patients with infarction of the septum and left ventricular anterior wall.[3,4] On the basis of the excitation process of the isolated human heart reported by Durrer *et al*,[5] this electrocardiographic finding is explained by the loss of the earliest excitation in the middle half of the left side of the interventricular septum because of septal infarction. In previous reports, however, the effects of the infarcted area in the neighbouring myocardium outside the septum could not be ruled out. We found that pure septal infarction induced the loss of initial R waves in the medial precordial leads and the loss of septal Q waves in the lateral precordial leads. Yamaki *et al* reported that electrical excitation of the right ventricle contributed to the formation of septal Q waves.[6] But in our patient we found that septal Q waves were not preserved despite a normal right ventricle. Further study will be required to clarify the contribution of the right ventricle to the genesis of septal Q waves.

In pure septal infarction we also found ST segment depression in the lateral and inferior leads, as well as ST segment elevation in leads V1–V3. Echocardiography and thallium-201 imaging showed no evidence of ischaemia in the lateral and inferior myocardium after infarction. This suggests that the ST segment depression in the lateral and inferior leads may be merely an electrical phenomenon—so called "reciprocal change". Evidence from our patient suggests that reciprocal change opposite to the ST segment elevation in the medial precordial leads caused by septal involvement may be one mechanism for the ST segment depression seen in the inferior leads during acute myocardial infarction of the left ventricular anterior wall.[7–9]

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Lymphatic abnormalities in Alagille's syndrome

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Abstract

Chylous pleural effusions developed in a patient with Alagille's syndrome who had dysplasia of the lymphatic system. Lymphatic abnormalities are not a recognised feature of Alagille's syndrome.

The features of Alagille's syndrome or arteriohepatic dysplasia as described by Alagille *et al*[1 2] and Watson and Miller[3] are congenital heart disease (particularly pulmonary artery stenosis), intrahepatic cholestasis, and dysmorphic facies. Other features have been described,[4] but abnormalities of the lymphatic system have not previously been reported.

Case report

A 19 year old man with Alagille's syndrome was admitted for investigation after a recent deterioration in exercise tolerance. He was born four weeks prematurely, the third child of elderly parents. He failed to thrive and at three months a blowing systolic murmur was noted. There was no history of cyanosis or feeding difficulties. At 6 months, a paediatric cardiologist made a clinical diagnosis of a ventricular septal defect. Cardiac catheterisation was performed when he was 18 months old. It showed an atrioventricular canal defect, equal right and left ventricular pressures, a gradient of 35 mm Hg across the pulmonary valve, and mild stenosis of the left pulmonary artery.

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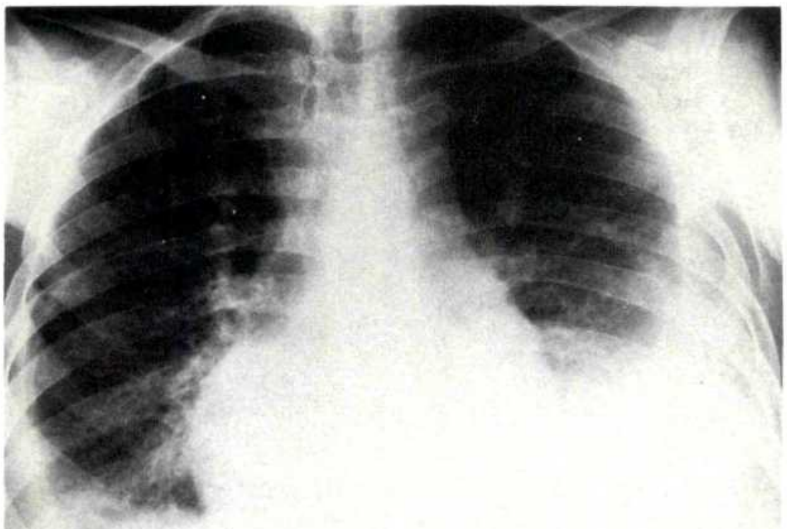


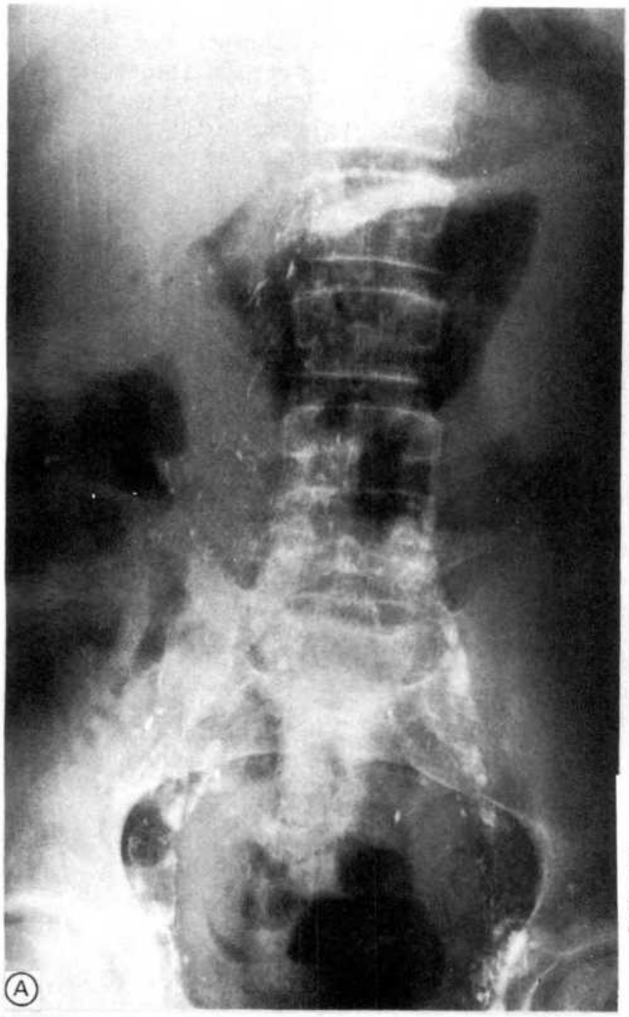
Figure 1 Chest radiograph showing bilateral pleural effusions.

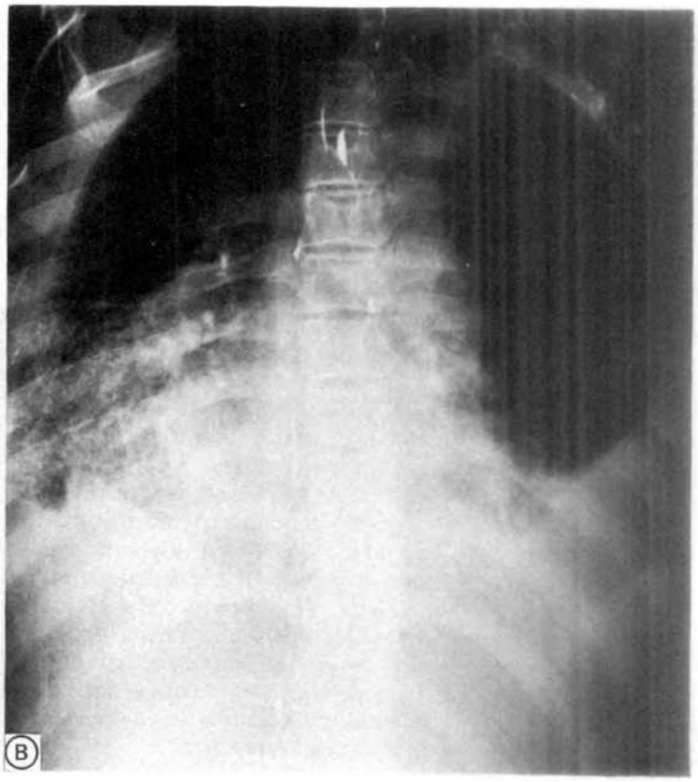
He achieved normal developmental milestones but height and weight remained below the third centile. At the age of eight the results of cardiac catheterisation were unchanged. At operation (aged 10), cardiomegaly was noted with considerable lymphatic engorgement in the anterior mediastinum, a large multiloculated cystic lesion containing lymph overlying the main pulmonary artery, and serpiginous distended lymphatic vessels surrounding the aorta. A large septum primum defect and cleft mitral valve were repaired. The tricuspid valve had no septal cusp whatsoever and a pulmonary valvotomy was performed.

After operation he remained small and on examination was slightly jaundiced with mild hepatosplenomegaly. When he was 14 he was referred to a paediatric endocrinologist, primarily for investigation of his short stature. He had a prominent forehead, deep set eyes, and a small pointed chin. Blood count and endocrine investigations were normal. The serum concentration of bilibrubin was raised but concentrations of other hepatic enzymes were normal. A liver biopsy was not performed because of persistently abnormal clotting. The bone age was delayed by four years and no vertebral anomalies were present. Fundoscopy showed prominent Schwalbe's lines and no retinal pigmentation. The findings of typical facies, congenital heart disease, mildly deranged liver function, and short stature indicated a diagnosis of Alagille's syndrome.

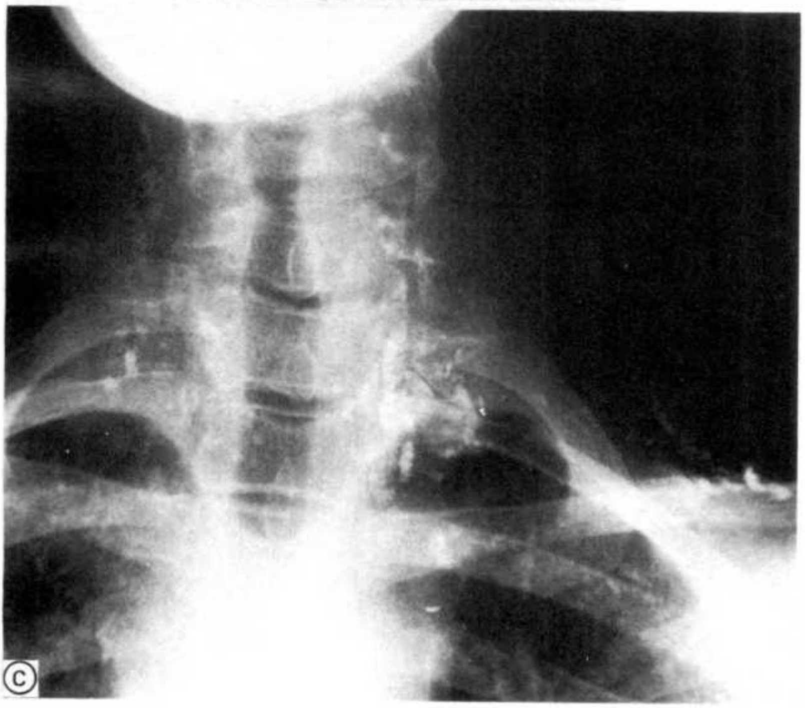
Five years later when he was 19 increasing breathlessness on exertion developed without cyanosis. A chest radiograph (fig 1) showed bilateral pleural effusions and he was admitted for investigation. The liver and spleen were mildly enlarged and there was continued rise of the serum concentration of unconjugated bilirubin. Serum concentrations of cholesterol and triglycerides and lipoprotein electrophoresis were all normal. The prothrombin time was prolonged (18 seconds, control 14 seconds) though the activated partial thromboplastin time, thrombin time, and antithrombin III activity were normal.

The pleural effusions were aspirated and found to be chylous. Lymphangiography showed considerable abnormalities of the lymphatic system. The lymphatic vessels in the right foot were very small and could not be cannulated. Lymphatic vessels in the left lower leg seemed normal. In the pelvis there was abnormal cross filling to the right with





igure 2 (A) Lymphangiogram film showing cross filling to right pelvic ymphatic vessels with contrast dispersed widely in the lumbar region. (B) Right lateral decubitus chest radiograph after lymphangiography showing pooling of contrast in ectatic lymphatic vessels and absence of the normal thoracic duct. (C) Lymphangiogram film showing contrast in nodes in the neck and left supraclavicular region.



tortuous and ectatic pelvic lymphatic vessels. Contrast was dispersed over a wide area around the lumbar spine (fig 2A). The thoracic duct was not clearly defined and ectatic thoracic lymphatic vessels were found, particularly in the decubitus position (fig 2B). Another unusual feature was filling of lymph nodes in the neck, left supraventricular, and axillary regions (fig 2C).

Treatment with a medium chain triglyceride diet was started and the effusions remain unchanged.

Discussion

Alagille's syndrome, or arteriohepatic dysplasia, affects several organ systems but abnormalities of the lymphatic system have not previously been described. The syndrome is probably not rare, because groups of patients as large as nine[3] to 15[2] have been reported. Though the cause remains unknown it seems to be genetic, with autosomal dominant inheritance and variable penetrance being supported by several reports of vertical transmission.[4]

A prominent feature of the syndrome is its clinical variability. Cholestasis may be mild, or absent in later years, with a range of cardiac lesions (though peripheral pulmonary stenosis is the most common). Diagnosis rests on the recognition of a constellation of features including hepatic abnormalities (neonatal jaundice and hypercholesterolaemia with a paucity of intrahepatic ducts) and congenital heart defects (peripheral pulmonary stenosis, pulmonary valve stenosis, and septal defects (both atrial and ventricular). Retinal abnormalities include Schwalbe's lines, Axenfeld's anomaly, and pigmentation. Abnormal vertebrae, impaired renal function suggesting a tubular defect, hypogonadism, hypothyroidism, absent reflexes, and poor academic performance have also been described.[5 6] Other syndromes of familial intrahepatic cholestasis may be clearly distinguished by their characteristic biochemical and physical features.

Patients with lymphatic hypoplasia usually present with lymphoedema. Congenital heart disease is rare in these patients (a 1·4% incidence was described in one series[7]) and no particular cardiac lesion predominates. Similarly, lymphatic hyperplasia was not associated with any particular congenital cardiac lesion though the incidence of 9·7% was far in excess of that expected in the general population (0·9%).

The patients we have described in this case report had many of the features of arteriohepatic dysplasia—though considerable abnormality of the lymphatic system was also present. This was noted by the surgeon at operation when the patient was eight, though the extent of lymphatic dysplasia did not become clinically apparent until large chylous pleural effusions rendered the patient breathless eleven years later.

Alagille's syndrome carries a better prognosis than other forms of intrahepatic cholestasis, with most patients surviving into adulthood. The abnormalities are rather more widespread than the name arteriohepatic dysplasia implies and lymphatic dysplasia should perhaps be added to the features of this syndrome.

We thank Dr G K Morris for permission to report this case.

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Br Heart J 1991;65:171–3

MEASUREMENT

Coronary sinus blood flow and coronary haemodynamic function in children: measurement by the continuous thermodilution method with coronary sinus cannulation via the femoral vein

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Abstract

In 19 children with Kawasaki disease without any cardiac sequelae the coronary sinus was cannulated via the femoral vein with a specially designed flow catheter and coronary sinus blood flow was measured by the continuous thermodilution method. There was a statistically significant positive correlation between coronary sinus blood flow and age, body surface area, and left ventricular mass, but coronary sinus blood flow per left ventricular mass (100 g) was negatively correlated with age, body surface area, and left ventricular mass. Coronary vascular resistance was negatively correlated with age, body surface area, and left ventricular mass.

Younger children require a much greater coronary blood flow per left ventricular mass and have a higher coronary vascular resistance than older children and adolescents. These results may indicate that coronary blood flow is less efficient in childhood than in adolescence or adulthood.

The supply of oxygen to the myocardium is determined mainly by the volume of the coronary blood flow. Therefore, measurement of coronary blood flow is a useful way of evaluating coronary lesions and myocardial ischaemia. Measurement of coronary blood flow and the evaluation of the coronary haemodynamic function by arteriography provides important clinical information for the management of children with the coronary sequelae of Kawasaki disease. However, there has been no systematic report on the coronary blood flow or coronary haemodynamic function in childhood because catheterisation of the coronary sinus is difficult in children. We have reported a technique for easier cannulation of the coronary sinus via the femoral vein during routine cardiac catheterisation.[1] To investigate the characteristics of coronary haemodynamic function in childhood, we measured the coronary sinus blood flow by the continuous thermodilution method using our specially designed flow catheter in children with Kawasaki disease without any sequelae.

Patients and methods

In the past two years, coronary angiography was carried out in 30 patients to detect the coronary sequelae of Kawasaki disease and to evaluate the coronary haemodynamic function. In the present study we analysed the findings in 19 (15 boys and four girls, aged 2 to 18 years (mean 8)) of the 30 patients who were shown to have normal coronary arteries despite echocardiographic evidence of dilatation. The interval from the onset of Kawasaki disease to the time of this study in the 19 patients ranged from one to 15 years (mean 6·7 years). The nature of the study was discussed with the patients' parents and then written consent was obtained.

After left ventricular angiography and selective coronary angiography, the coronary sinus flow catheter (fig 1A) (Webster Co, CCU-7U-90B), which was designed in our laboratory, was introduced through the femoral vein into the coronary sinus by a technique reported previously[1] (fig 1B). The coronary sinus flow catheter has an injection orifice at the tip and an external thermistor 12 mm from the tip. The position of the catheter was confirmed by angiography. In addition, a pigtail catheter was inserted through the femoral artery into the ascending aorta. Coronary sinus blood flow was measured by the continuous thermodilution method[2] >30 minutes after the angiographic studies. The coronary vascular resistance was calculated as the ratio of mean arterial pressure (mm Hg) to coronary sinus blood flow (ml/min). Left ventricular mass was calculated from the left ventricular angiogram.[3]

Results

In the 19 patients, coronary sinus blood flow at rest increased significantly with age: age 2–4 years, 51·9 (10·4) (mean (SD)) ml/min; age 5–9 years, 75·8 (8·7) ml/min; age 10–18 years, 102·4 (17·7) ml/min (fig 2A). Coronary sinus blood flow was positively correlated with age, body surface area, and left ventricular mass

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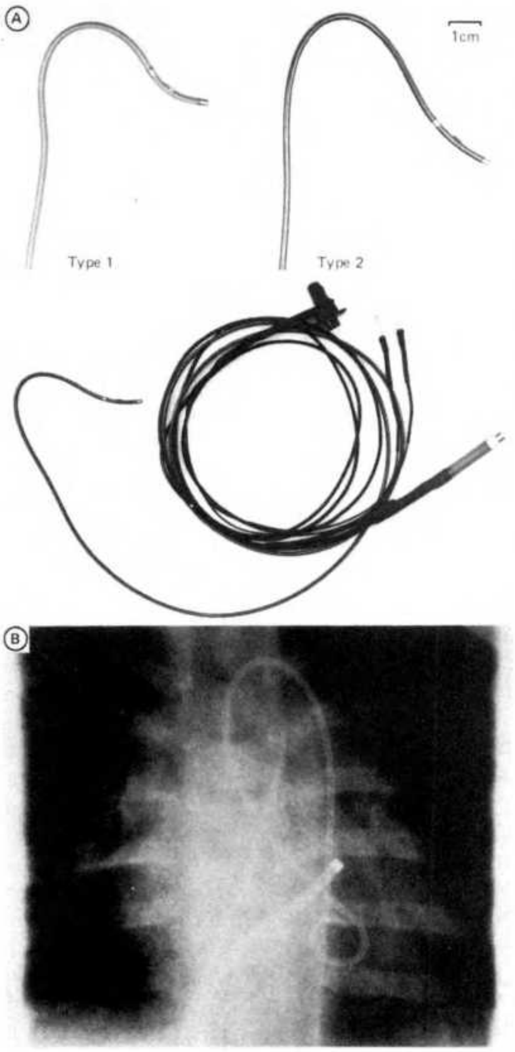

Figure 1 (A) Specially designed coronary sinus flow catheters; type 1 was for young and older children and type 2 for adolescents and adults. (B) Coronary sinus flow catheter inserted through the femoral vein into the coronary sinus.

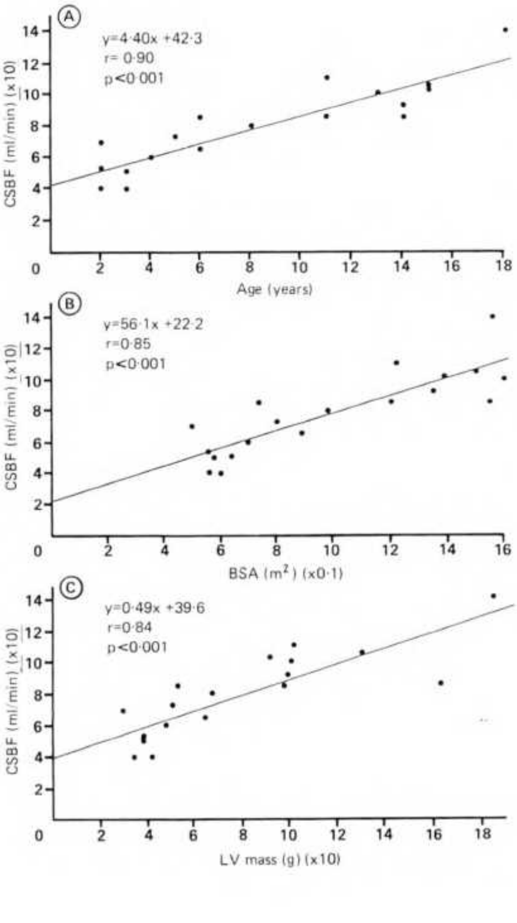

Figure 2 Relations between coronary sinus blood flow (CSBF) and aging (A), body surface area (BSA) (B), and left ventricular (LV) mass (C).

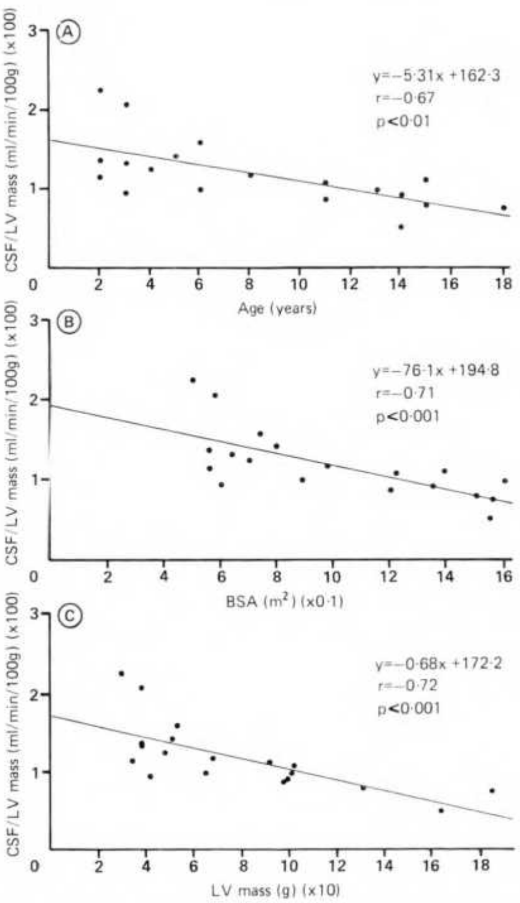

Figure 3 Relations between coronary sinus blood flow per 100 g left ventricular mass (age) (A), body surface area (B), and left ventricular mass (C).

(fig 2). Coronary sinus blood flow per left ventricular mass (100 g), however, was negatively correlated with age, body surface area, and left ventricular mass (fig 3). Furthermore, in the 19 patients, coronary vascular resistance was negatively correlated with age (fig 4), body surface area ($r = -0·55$, $p < 0·02$), and left ventricular mass ($r = -0·53$, $p < 0·02$). The rate-pressure product did not correlate with age ($r = -0·20$, $p < 0·5$) or coronary sinus blood flow ($r = 0·22$, $p < 0·5$), and the coronary sinus blood flow did not correlate with heart rate ($r = -0·44$, $p < 0·1$).

Discussion

This study showed that coronary sinus blood flow in childhood was positively correlated with age, body surface area, and left ventricular mass. Coronary sinus blood flow in adults

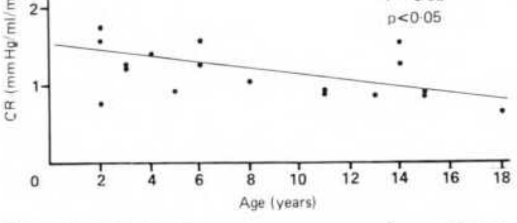

Figure 4 Relation between coronary vascular resistance (CR) and age.

ranged from 90 to 130 ml/min.[2,4–6] Our findings indicate that coronary sinus blood flow in children over 10 years of age was comparable to that in adults. But younger children required a greater coronary sinus blood flow per left ventricular mass than older children or adolescents. Furthermore, the coronary vascular resistance in early childhood was higher than in late childhood and adolescence. These results suggest that coronary blood flow in early childhood was less efficient than in late childhood or adulthood. Therefore, these characteristic coronary flow patterns should be borne in mind during the evaluation of coronary haemodynamic function in childhood.

We thank the following colleagues for participating in this study Shosei Hayashi, Eikan Koh, Masao Nakagawa, Toshiyuki Itoi, Isao Shiraishi, Takashi Hayano, Hiroshi Fukumochi, Koichi Sakata

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BRITISH CARDIAC SOCIETY NEWSLETTER

All cardiologists, both in the principal centres and in district general hospitals, should by now have received a form to complete on cardiac registrars. We are all bedevilled these days by forms that demand action, and I do not imagine that this latest one from the British Cardiac Society and the Specialist Advisory Committee will have been any more welcome than all the others that land so regularly on our desks Unfortunately they are a necessary evil in our brave new world and we ignore them at our peril — or that of our departments. Fortunately, the information we are seeking now is simple; it must be provided by all consultant cardiologists who wish to have a post at "registrar" level considered for the first part of the new six year programme. The changeover from the existing less formal arrangements will occur over a year or so, but we hope that most new appointments will now be made under the new scheme. For those in England and Wales application must also be made to the Joint Committee on Higher Medical Training office at the Royal College of Physicians; other arrangements will be made for Scotland and Northern Ireland. Some details were given when the forms were sent out, but any who are unsure how to proceed should contact Peter Sleight or Douglas Chamberlain. At the time of writing, the total number of posts at registrar level has not been agreed, but we are reasonably optimistic that we will have enough "protected" for the specialty to match the requirement for subsequent senior registrar vacancies. Selection may not be easy and many difficulties are yet to be resolved. No post can be finally approved, however, without inspection by the Specialist Advisory Committee. Soon, incidentally, it will be time to conduct another census of senior registrars. We are aware that some of those now or recently in post have been slow to apply for a training number with a view to accreditation. To neglect this is unwise.

The number of senior registrar positions in cardiology approved by the Joint Planning Advisory Committee is 60. Of these, eight are now reserved for paediatric cardiology (with two not taken up because of administrative delays) and two are reserved for part time appointments for up to four individuals (at least one of which has not been allocated). There are 10 posts set aside for research under the aegis of the Association of Medical Charities, the Medical Research Council, and Regional Health Authorities. But these are not speciality specific. In other words, we have no guarantee that the 10 research posts will go to cardiologists: we have merely contributed an arbitrary share of a pool from which the posts in all specialities are taken. We have some protection from the mere play of chance, however, because six of the 10 are at present allocated to the British Heart Foundation Even from here — and reasonably — research applications will be successful only on the basis of scientific merit. Those who are successful may not be training for consultant posts in cardiology and indeed may not be cardiologists at all. Thus we have rigid control of the numbers of senior registrar posts (calculated on the basis of expected retirements from the consultant grade plus an allowance for historical growth), yet 20% of the allocation (10 of 50) is beyond our control. This curious system seems a total abrogation of the stated intention to achieve a balance Only 40 training posts are available in England and Wales for senior registrars (and academics of equivalent status) in adult cardiology.

Peter Sleight and Douglas Chamberlain (as chairman of the Training and Manpower Committee) discussed the Joint Planning Advisory Committee process in an informal meeting with two representatives of the Department of Health on the 4 December. We were courteously received and given useful advice on submissions· problems were discussed but could not be resolved in that forum. Another useful meeting took place a few weeks earlier with the secretary of the Association of Medical Charities, but again problems could be defined better than they could be solved.

The publicity over the Björk-Shiley valves continues. We understand the motives for the current moves to alert patients who have the vulnerable valves, but it seems regrettable that there should be a need further to heighten their level of anxiety. One of the lessons of the current problem has been the difficulty in discovering for many patients the details of prosthetic valves in situ. This information should be readily available from the patients' notes, but for many reasons this system can fail. Many patients do carry cards issued by the valve manufacturer, but the process to obtain a card is not totally simple and frequently fails We believe that all patients with artificial heart valves should be given a standard card or bracelet while they are still in hospital. No approach has yet been made for cooperation from the manufacturers, but pacemaker companies were very helpful when similar issues were discussed several years ago. Do members feel this should be pursued?

We end this newsletter on a sad note. Many will now be aware of the sudden death on 5 January of Professor Attilio Reale who was President of the European Society of Cardiology He became president at the Stockholm meeting: many will have heard his speech at the assembly when he looked forward to his period in office, which was tragically cut short. We hope to write more of this next month and also of the changes that will be necessary within the European Society.

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NOTICES

1991

The Annual Meeting of the **British Cardiac Society** will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May. The closing date for receipt of abstracts was 10 December 1990.

An international workshop on **Coronary Surgery: Clinical and Basic Perspectives** organised by the Department of Cardiac Surgery of the University of Sheffield and the British Society for Cardiovascular Research will be held in Sheffield on 17 May: Mr G D Angelini, FRCS, Department of Cardiac Surgery, Northern General Hospital, Sheffield S5 7AU (0742 434343).

The 5th annual meeting of the **Mediterranean Association of Cardiology and Cardiac Surgery** will be held in Alexandria on 23 to 27 September: Professor M El-Fiky, Cardiac Surgery Department, Ain Shams Faculty of Medicine, Abbassia, Cairo, Egypt (202 834981/835495; Fax 202 834981).

The 5th international symposium on **Calcium Antagonists: Pharmacology and Clinical Research** will be held in Houston on 25 to 28 September: Organizing Secretariat, Giovanni Lorenzini Medical Foundation, c/o Dr Marjorie G Horning, Baylor College of Medicine, Room 826 E, One Baylor Plaza, Houston, Texas 77030, USA (713 797 0401; Fax 713 796 8853) and Organizing Secretariat (for Europe), Fondazione Giovanni Lorenzini, Via Monte Napoleone, 23-20121 Milan, Italy (02 78 36 68-76 00 22 67; Fax 02 78 15 11).

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BRITISH
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Editorial

Coronary thrombolysis: round two and beyond

Within a remarkably short time of the re-emergence of interest in thrombolytic treatment for acute myocardial infarction the efficacy of this approach was confirmed in several large randomised trials of streptokinase,[1 2] anistreplase (anisoylated plasminogen streptokinase activator complex, APSAC),[3] alteplase (recombinant tissue plasminogen activator),[4] and streptokinase with adjunctive antiplatelet treatment with aspirin.[2] Despite their considerable physicochemical and biological differences, treatment with any of these thrombolytic agents is expected to reduce mortality by 25% to 40% with added aspirin (at least when added to streptokinase), and the early gains in survival persist for at least 12 months.

These round one single thrombolytic trials have given us reassurance about the relative safety of such treatment in properly selected patients and have indicated what the risks are—a *small* increased risk of stroke, major bleeding, and allergic reactions (with streptokinase and anistreplase). They have also raised a host of issues that require further study. For instance, is there truly a crucial time window for maximum (or for any) benefit? Will aspirin enhance the effects of alteplase as well as the effects of streptokinase? Does the addition of aspirin make the coadministration of heparin superfluous? Is re-exposure to streptokinase within (say) six months truly dangerous or ineffective or both because of residual antibody titres? Is one thrombolytic agent better than another? Has combination thrombolytic therapy anything unique to contribute?

Comparison trials

Some of these questions may be answered in round two by the direct comparison trials, the first pair of which have recently been published.[5 6] In these open trials (the first, GISSI-2, is a large subset trial of the International Study Group) over 20 000 patients within six hours of onset of major symptoms were randomised to receive the current standard dose regimens of either streptokinase (1·5 megaunits intravenously over 30–60 minutes) or alteplase (10 mg intravenous bolus, 50 mg intravenously in the next hour, and 20 mg intravenously in each of the next two hours). All patients were given oral aspirin from admission and half were randomly allocated to receive subcutaneous heparin, 12 500 units twice daily, beginning 12 hours after the onset of thrombolysis.

The results at face value provide gratifying reading for health economists—no significant differences for major cardiac clinical events, indices of infarct size, left ventricular function, reinfarction, or death by the end of hospital stay (mean 13 days). There were more strokes with alteplase than with streptokinase (1·3% *v* 1%), but more major bleeds with streptokinase than with alteplase (0·9% *v* 0·6%) and with heparin (1%) versus no heparin (0·5%). Heparin did not affect the incidence of stroke or reinfarction.

Is heparin still needed?

These trials have confirmed both the comparative efficacy and safety of adding oral aspirin to either streptokinase or alteplase. The heparin question, however, may have been confused rather than clarified, because without heparin the in-hospital death rates were streptokinase 9·2% and alteplase 8·7%, whereas with heparin they were streptokinase 7·9% and alteplase 9 2%. The streptokinase results resemble those reported in ISIS-2 where, though heparin was an optional treatment, those patients allocated to streptokinase plus aspirin who were given heparin had a lower death rate than those who were not, albeit at a slightly higher risk of bleeding. In the trial reported by the International Study Group, however, the mortality patterns were already established in the 12 hours before heparin was started, though critics have suggested that the delay before heparinisation disadvantaged the alteplase group because this agent's shorter half life and lower systemic hypocoagulant effect exposed patients in that group to reocclusion. Further, although the dose and mode of heparin administration in the trial reported by the International Study Group were considered to be both safe and efficacious,[7 8] other evidence, both clinical and experimental, suggests otherwise.[9 10]

This concept of post-thrombolytic vulnerability to reocclusion after alteplase without heparin is supported by several clinical patency studies. In TAMI-3 (Thrombolysis in Acute Myocardial Infarction), patients were randomised to alteplase with or without heparin and there was no difference in the early (90 minute) infarct vessel patency (79%), but since all the patients subsequently received intravenous heparin the question of further deferment was not addressed.[11] In the heparin and aspirin reperfusion trial, 204 patients received alteplase plus either low dose aspirin (80 mg) or intravenous heparin and the infarct vessel patency rates at 15 hours were 52% and 82% respectively.[12] In a similar but smaller study, Bleich and colleagues reported 55–59 hour patency rates of 44% with alteplase alone, compared with 71% when alteplase was coadministered with heparin (5000 unit bolus, then 1000 units per hour intravenously).[13]

The largest study to examine this issue was reported by Professor de Bono for the European Cooperative Study Group at the recent European Congress of Cardiology in Stockholm. Six hundred and fifty two patients with evolving myocardial infarction were randomised double blind to receive alteplase 100 mg plus aspirin plus either immediate intravenous heparin (5000 unit bolus followed by 1000 units per hour until angiography) or placebo. Coronary angiography at 48–120 hours (mean 81 hours) showed TIMI (Thrombolysis in Myocardial Infarction) grade 2 or 3 perfusion of 83% in the heparin group compared with 75% in the placebo group—a significant but less dramatic difference than in the study reported by Bleich *et al*. There were no differences in other clinical variables. Finally, the random discontinuation of intravenous heparin at 24 hours and its replacement with aspirin plus dipyridamole had no deleterious impact on the pre-discharge rates for coronary artery patency (79%).[14]

Though comparable studies have not been reported with streptokinase, the message for alteplase seems to be that some form of anticoagulation (not just aspirin) may be essential to maintain the high patency rates. If indeed patency is more quickly achieved with intravenous alteplase than with streptokinase,[15] and if early patency is advantageous and its effect measurable, then a re-run of the trial reported by the International Study Group but with early heparin should give the answer. However, the other large (more than 40 000 patients) round two, trial comparing alteplase, streptokinase, and anistreplase may clarify this issue, though even in this (ISIS-3) trial administration of heparin is deferred for four hours.

Round three studies

Is it possible and safe to try to exploit the virtues of two (or more) thrombolytic drugs given either together or sequentially—such as an initial high dose alteplase to achieve maximum patency as quickly as possible,[16] followed by streptokinase or urokinase to maintain systemic hypocoagulation with less clot specificity, which may lessen the haemorrhagic stroke rate. Some clinical data commend this dual approach. The TAMI investigators reported a reocclusion rate as low as 2% when alteplase was given with urokinase, compared with 12% for alteplase and 7% for urokinase alone.[17] A preliminary study to compare the results with alteplase and streptokinase and alteplase alone has reported similar figures.[18] Initial patency rates do not seem to be greatly improved by dual therapy and in the large mortality trials reocclusion rates of 10–15% are certainly not clinically recognised as reinfarctions.

The prospect of giving two thrombolytic drugs plus aspirin and simultaneous heparin is awesome, but such trials are planned and pilot studies are in progress. In the mean time we are eager to see whether ISIS-3 delivers a message substantially different from that of the International Study Group and in 1992 we should have the results of LATE (Late Assessment of Thrombolytic Efficacy), which is a double blind study randomising patients at 6–24 hours from the onset of symptoms to either placebo or alteplase; both treatment groups are also being treated with oral aspirin and early heparin.

Re-exposure to streptokinase

The question of re-exposure to streptokinase hinges on the importance of persisting streptokinase neutralising antibodies. Though the pretreatment titres—presumably residua from previous streptococcal infections—do not seem to correlate with either 90 minute infarct vessel patency or the likelihood of hypotensive reactions after either streptokinase or anistreplase, the titre of antibodies rises rapidly and remains high enough at six months "theoretically" to neutralise half a standard 1·5 megaunit dose of streptokinase or anistreplase.[19 20] Clearly the measurement of pretreatment antibodies is not necessary in patients who have never received streptokinase or anistreplase, nor is it practicable in those who have within, say, the previous 6–12 months.

This is a far from theoretical dilemma because we need to know whether re-exposure to streptokinase at any time is either dangerous or ineffective or both. The often quoted solution to use alteplase if retreatment is necessary conveniently avoids the question. But how to solve it? Would anyone collaborate in a randomised trial of streptokinase or alteplase in patients who have received streptokinase in, say, the previous six months? In such a trial various pretreatment antibodies against streptokinase would be measured and because a large enough trial might be impossible coronary artery patency would need to be a surrogate for mortality. Patients would need to be stratified according to time from initial exposure to streptokinase. Without such a trial alteplase will presumably occupy the re-exposure niche. For most other patients, however, the "gold standard" thrombolytic therapy at present remains streptokinase plus aspirin—plus heparin?

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ORIGINAL ARTICLES

Circadian variation in the frequency of onset of chest pain in acute myocardial infarction

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Abstract

The time of onset of chest pain was studied prospectively in 1154 consecutive patients admitted to a coronary care unit with myocardial infarction during a five year period. Statistical analysis confirmed a previous finding in a retrospective study of a bimodal frequency distribution with peaks in the time of onset of chest pain between 2330 and 0030 hours and between 0630 and 0830 hours.

Many cardiac disorders[1] including sudden death,[2] angina,[3] and asymptomatic myocardial ischaemia[4 5] are more frequent at the normal waking time. Studies have shown that the onset of acute myocardial infarction also often occurs at this time.[6–8] However, in a retrospective study of the time of onset of chest pain in myocardial infarction[7] our data also suggested a bimodal distribution, with a secondary peak around midnight. Though several studies found convincing evidence for a second, late evening peak[6 9–11] others have not found such a pronounced midnight peak. We have, therefore, completed a five year prospective study of the time of onset of chest pain in 1154 patients admitted to a coronary care unit with a myocardial infarction.

Patients and methods

PATIENTS

Since the inception of the coronary care unit of Leicester General Hospital in 1976 accurate records of all patients admitted have been kept on a card index. The date and time of onset of chest pain and admission to and discharge from the unit together with electrocardiographic and cardiac enzyme changes, complications, and treatment have been recorded separately from each patient's hospital notes.

During a five year period (1984–89) 4975 patients were admitted to the coronary care unit. In 1716 (34·5%) of these an acute myocardial infarction was diagnosed on the basis of at least two of the following criteria: (*a*) myocardial ischaemic pain lasting > 30 minutes, (*b*) creatine kinase concentration more than twice the upper limit of normal, and (*c*) electrocardiographic evidence (Minnesota code) of acute infarction. Five hundred and sixty two patients were excluded because they had no pain, were admitted to the coronary care unit > 24 hours after symptoms began or because data could not be collected on arrival because of uncertainty, language difficulties, or collapse. The time of the onset of chest pain was taken to the nearest hour.

STATISTICAL ANALYSIS

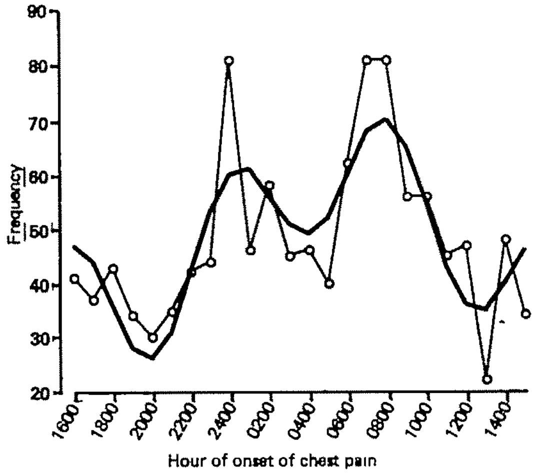
When the frequency of chest pain over time was plotted there were two major peaks at 2330–0030 hours and at 0630–0830 hours. The distribution over time was not uniform ($\chi^2 = 116{\cdot}3$, df = 23, $p < 0{\cdot}0001$). A harmonic regression analysis gave a statistically significant fit ($p < 0{\cdot}001$, $R^2 = 64\%$) with the equation: frequency of onset $= 48{\cdot}1 + 0{\cdot}94 \cos(2\pi t/24) + 13{\cdot}1 \sin(2\pi t/24) + 11{\cdot}2 \cos(6\pi t/24) + 0{\cdot}83 \sin(6\pi t/24)$, where t = time of day in hours.

Results

In 1154 patients with proven myocardial infarction we found two significant peak times for the onset of chest pain: 2330–0030 hours and 0630–0830 hours (figure). This five year prospective study confirmed the previously reported bimodal distribution.

Discussion

There is a clear circadian pattern to myocardial ischaemic chest pain. Several studies reported a significant rise in frequency during the early morning hours and some report a smaller secondary increase in frequency during the afternoon and late evening.[6 9–11] As far as we are aware, however, this and our earlier study[7] are the only ones to report an increased frequency



Hourly frequency of onset of chest pain in acute myocardial infarction. Open circles represent the frequencies and the continuous line the fitted values.

at midnight. Why chest pain is more common at these times is unknown, though recent studies on the circadian rhythm of onset of myocardial infarction have suggested that the morning peak of incidence is related to other known daily rhythms.[4 8] An obvious explanation for the early morning peak is the increase in physical and mental stress after waking.[12] Sympathetic activity increases after waking and plasma concentrations of catecholamine increase. Cortisol concentration peaks early in the morning, generally before waking, and it remains high but falls during the period after awakening.[13] Systemic arterial pressure,[14] coronary vascular tone,[15] and platelet aggregability[16] also increase. Though fibrinolytic activity is low during sleep and still reduced soon after awakening it rises during this time.[17]

The reasons for the midnight peak are less clear, though it could be linked to dilatation of the left ventricle at lower heart rates in the supine position with an increase in filling pressure, which has been reported to be associated with nocturnal ischaemia.[18] Patients with resting angina and severe coronary stenosis often exhibit a nocturnal decline in their ischaemic threshold: the incidence of angina at rest was highest between 2000 and 2300 hours.[19] There is evidence of differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction: in patients with a history of congestive heart failure, or with non-Q wave infarction there was a pronounced peak only in the evening.[20] The midnight peak may reflect altered circadian rhythms caused by late working hours, or individual behavioural differences. We are now collecting information on these differences and normal waking time and daily activities for another study.

There have been isolated reports of an evening peak, though not all studies have shown it to be significant. It is likely that a meta-analysis of all major studies would show that this peak is statistically significant, but the validity of the present analysis does not depend on it. It is unlikely that the same systematic bias operated for five years. The present data set (n = 1154) is one of the largest reported. The result of circadian analysis completely confirms the findings obtained in a large retrospective data set (n = 1099) obtained from the same location and processed by the same unit.[7]

Patients are admitted directly to the coronary care unit via the emergency ambulance service. The average delay between reporting onset of symptoms and admission to the unit is about 30 minutes. The two main coronary care units admit on seven days a week from all parts of the city of Leicester and surroundings. The number of patients admitted at Leicester General Hospital is roughly 50% of the total, without any geographical, sex, or age bias.

We considered the possibility that patients presenting with nocturnal chest pain were overrepresented in our study group. But those taken ill at night are less likely to call help immediately and thus more likely to die before reaching the coronary care unit. As in most previous studies, we used subjective reports of onset of chest pain. None the less, data suggest that, for acute myocardial infarction, subjective reports are consistent with objective measures.[8] It is unlikely that errors were introduced by patient recall because in most patients the data were carefully checked for accuracy with the spouse.

The observation of a circadian variation in the frequency of onset of chest pain in acute myocardial infarction has obvious therapeutic implications. It seems logical to target pharmacological treatment on the underlying physiological changes responsible for ischaemic events in those patients at risk. Ideally, this treatment should offer protection during the night and early morning hours.

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A critical threshold of exercise capacity in the ventilatory response to exercise in heart failure

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Abstract

During exercise patients with chronic left heart failure ventilate more than normal individuals at the same workload; the ratio of minute ventilation to minute production of carbon dioxide ($\dot{V}E/\dot{V}CO_2$) is increased. The relation between increased $\dot{V}E/\dot{V}CO_2$, severity of heart failure, and exercise capacity has not been defined. $\dot{V}E/\dot{V}CO_2$ was measured in 47 patients with chronic left heart failure (New York Heart Association grades II and III) and in 1009 healthy controls. Exercise capacity was assessed by peak oxygen consumption ($\dot{V}O_2$max) during progressive exercise. In the controls $\dot{V}O_2$max ranged from 25 to 93 ml/kg/min; $\dot{V}E/\dot{V}CO_2$ was 17–36 and did not correlate with $\dot{V}O_2$max. In chronic left heart failure the $\dot{V}O_2$max ranged from 9 to 29 ml/kg/min; $\dot{V}E/\dot{V}CO_2$ was 22–42 and correlated strongly with $\dot{V}O_2$max. End tidal carbon dioxide and respiratory rate at peak exercise were similar in the controls and patients with chronic left heart failure. The increase in $\dot{V}E/\dot{V}CO_2$ on exercise in chronic left heart failure indicates increased physiological dead space, presumably caused by a ventilation-perfusion mismatch. In the controls and patients with chronic left heart failure the relation of $\dot{V}E/\dot{V}CO_2$ to $\dot{V}O_2$max was curvilinear with a threshold of $\dot{V}O_2$max below which $\dot{V}E/\dot{V}CO_2$ started to rise above the normal range. This point of inflection may be explained by the existence of a critical level of cardiac function necessary to perfuse adequately all lung zones on exercise.

Dyspnoea is a major symptom of chronic left heart failure and may severely limit the exercise capacity of the patient.[1] The pathophysiological basis of this symptom is not understood, though many explanations have been proposed. In patients with acute pulmonary oedema a rapid rise in pulmonary venous pressure leads to the accumulation of interstitial fluid, decreased lung compliance, and increased airway resistance.[2 3] This simple explanation, however, does not apply to patients with chronic left heart failure, in whom there is no apparent relation between dyspnoea and pulmonary venous pressure.[4 5]

Numerous studies have reported an increased ventilatory response to exercise in heart failure: patients with chronic heart failure ventilate more than healthy controls at the same external workload.[6–8] This increased ventilation may be expressed as the ratio of the minute ventilation to the minute production of carbon dioxide ($\dot{V}E/\dot{V}CO_2$), which standardises for any differences in metabolic rate.[9 10] It has recently been suggested that the increased $\dot{V}E/\dot{V}CO_2$ is associated with dyspnoea.[11] The exact relation between the value of the $\dot{V}E/\dot{V}CO_2$ ratio, the functional state of the patient, and the level of dyspnoea is not known, however. We have therefore examined the relation between $\dot{V}E/\dot{V}CO_2$ and exercise capacity across a range of severity of chronic heart failure and in a large group of healthy controls of different levels of fitness to determine the relation between exercise capacity, exercise hyperpnoea, and the efficiency of gas exchange.

Patients and methods

PATIENTS

We recruited 47 patients with chronic left heart failure in New York Heart Association categories II or III from outpatient clinics. Impaired left ventricular function was assessed both by radionuclide gated blood pool scanning and by echocardiographic determination of ejection fraction; the left ventricular ejection fraction by both methods was $<50\%$. Patients with valvar heart disease were excluded. There was no evidence of primary lung disease as judged by history, clinical examination, and chest *x* ray, and each patient achieved at least 70% of the predicted normal values on lung function tests, static lung volumes, airways resistance, and carbon monoxide gas transfer. Patients with disturbance of balance or with musculo-skeletal problems that might limit exercise were excluded. The project was approved by the local ethics committee and all patients gave written consent.

Healthy individuals with no history of cardiopulmonary disease were recruited from a health screening service. Physical examination, resting and exercise electrocardiograms, chest *x* ray, and lung function tests were all normal.

EXERCISE TESTING

All subjects performed progressive maximal symptom limited exertion. Pulse, respiratory rate, blood pressure, and the 12 lead electrocardiogram were recorded in each stage. Subjects performed a familiarisation maximal test with expired gas analysis 2-14 days before the study. Patients were given the usual cardiac medications that day. All subjects were tested at least two hours after eating.

Table 1 Main characteristics (range (median)) of patients and healthy controls

	Patients (n = 47)	*Controls (n = 1009)*
Age (yr)	47–78 (65)	25–70 (45)
Body mass index	18 2–29·8 (22 7)	13·7–45 6 (24 7)
LVEF (%, by MUGA)	5–48 (24)	—
FEV_1 (l)	1·2–3·7 (2 3)	1·5–6·4 (3·8)
FEV_1 (% predicted)	76–124 (92)	75–129 (98)
FVC (l)	1·5–5 6 (3 1)	2·3–7·6 (4·7)
FVC (% predicted)	71–117 (83)	77–128 (99)
VA (l)	3 2–7·9 (5 4)	4 7–11 9 (7·4)
VA (% predicted)	71–125 (94)	74–132 (102)

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction determined by radionuclide gated blood pool scanning; MUGA, multigated acquisition; VA, alveolar volume determined as lung volume accessible to helium gas.

Expired gases were analysed at rest until a steady state was achieved, and then continuously during exercise and the recovery phase. Subjects wore a mouthpiece with low resistance Hans Rudolf spiral non-return valve and there was a low volume of dead space in the circuit. Expired gas passed through a mixing box and was sampled by four channel mass spectrometer (AirSpec MGA200), with the output passing to analogue-to-digital converter and on line computer. Ventilation was measured by argon dilution.[12] Oxygen production (ml/kg/min), carbon dioxide production (ml/kg/min), and minute ventilation (l/min) were averaged and calculated every 10 seconds by the on line computer during the test. We analysed the results by taking mean values over the last minute of exercise. Respiratory rate and end tidal carbon dioxide were recorded over the last 30 seconds of each stage and over the last minute of exercise.

End tidal carbon dioxide was measured at the mouthpiece by an infrared capnograph (Godart) and a corrected estimate of mean arterial P_{CO_2} was obtained by the Jones formula.[13] Arterial oxygen saturation was monitored by pulse oximetry at the ear lobe (Radiometer). In a subgroup of 10 patients the oxygen saturation and end tidal carbon dioxide were validated against arterialised ear lobe blood samples analysed in a Radiometer ABL3 machine.

Measurements of $\dot{V}_E/\dot{V}_{CO_2}$ and of end tidal carbon dioxide were used to calculate the ratio of dead space ventilation to total minute ventilation ($\dot{V}_D/\dot{V}_E$) according to the Bohr equation.[14 15] We calculated tidal volume and thus the mean dead space per breath (V_D/breath) from the measured respiratory rate and minute ventilation:

$$V_T = \dot{V}_E/RR$$

$$V_D/\text{breath} = V_T \times (\dot{V}_D/\dot{V}_E).$$

Table 2 Reproducibility of respiratory measurements on repeat testing in patients

Measurement	*Mean difference (test 3 − test 2)*	*SD of differences*
Exercise duration (min)	+0·26	±1 62
Peak oxygen consumption ($\dot{V}O_2$ max) (ml/kg/min)	−0·19	±1 53
Peak ventilation (l/min)	−0 23	±6·7

REPRODUCIBILITY

We determined the reproducibility of ventilatory measurements on repeated testing by performing a third non-invasive maximal exercise study 1–5 weeks after the second study in all 47 patients with heart failure. Reproducibility data are presented as the mean difference (test 3 − test 2) ± the SD of the differences.

ANALYSIS

In the 1009 controls univariate relations between the variables were assessed by Pearson's product-moment correlation coefficient. Adjustment for the possible confounding effects of age and weight (body mass index) was made by multiple linear regression analysis. We examined the magnitudes of weak but statistically significant correlations with $\dot{V}O_2max$ within the large group of controls by dividing the group into deciles of $\dot{V}O_2max$ and calculating the mean value of the given variable for each decile.

We used non-parametric statistical analysis for the small group of patients with chronic left heart failure. Values of variables are given as median and range. Correlations were examined by the Spearman rank correlation coefficient R.

Results

GROUP CHARACTERISTICS

The patients were aged 47–78 (median 65) and the normal healthy subjects were aged 25–70 (median 45). Though the patients with chronic left heart failure tended to be older this difference was not statistically significant. Static lung volumes were all approximately 80–85% of the predicted normal value in the patient group (table 1).

REPRODUCIBILITY STUDIES

There were no significant differences between resting or exercise values for any of the ventilatory variables between the two studies in the 47 patients with chronic left heart failure. Table 2 gives the mean differences and the standard deviation of the differences.

PATIENTS WITH CHRONIC HEART FAILURE

Peak oxygen consumption ($\dot{V}O_2max$) ranged from 9 to 29 (median 14) ml/kg/min. Table 3 gives the results of exercise testing and the respiratory variables calculated from the exercise data. The ratio $\dot{V}_E/\dot{V}_{CO_2}$ at peak exercise was 22·3–41·6 (median 29·8). $\dot{V}_E/\dot{V}_{CO_2}$ correlated significantly with $\dot{V}O_2max$: $R = -0{\cdot}53$, $p < 0{\cdot}002$. Figure 1 shows the curvilinear relation; at values of $\dot{V}O_2max$ more than 18–20 ml/kg/min $\dot{V}_E/\dot{V}_{CO_2}$ was within the normal range, but at values less than this $\dot{V}_E/\dot{V}_{CO_2}$ rose steeply as $\dot{V}O_2max$ fell. When $\dot{V}O_2max$ was less than 20 ml/kg/min the correlation between $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}O_2max$ is even stronger: $R = -0{\cdot}62$, $p < 0{\cdot}001$ (linear regression equation:

$$\dot{V}_E/\dot{V}_{CO_2} = 40{\cdot}7 - 0{\cdot}7(\dot{V}O_2max)).$$

The ratio $\dot{V}_D/\dot{V}_E$ at peak exertion also correlated with $\dot{V}O_2max$: $R = -0{\cdot}58$, $p <$

Table 3 Results (range (median)) of cardiopulmonary exercise testing in patients and healthy controls

Variable	*Patients (n = 47)*	*Healthy controls (n = 1009)*
Exercise duration (min)	3–15 (7)	8–22 (15)
$\dot{V}O_2$ max (ml/kg/min)	9–29 (14)	25–93 (42)
Peak ventilation (l/min)	18–73 (33)	35–137 (79)
Peak respiratory rate (per min)	21–36 (28)	24–38 (30)
End tidal CO_2 at peak exertion (%)	4·5–5·6 (5·0)	3·7–6·1 (5·1)
$\dot{V}E/\dot{V}CO_2$	22·3–41·6 (29·8)	16·9–35·8 (25·0)
$\dot{V}D/\dot{V}E$	0·14–0·55 (0·35)	0·02–0·65 (0·26)
VD/breath (ml)	149–843 (393)	490–1740 (660)

$\dot{V}O_2$ max, peak oxygen consumption averaged over the final minute of a maximal exercise test; $\dot{V}E/\dot{V}CO_2$, ratio of minute ventilation to minute production of carbon dioxide; $\dot{V}D/\dot{V}E$, ratio of dead space ventilation to total ventilation, VD/breath, dead space ventilated per breath.

0·001. Dead space per breath (VD/breath) at peak exertion correlated weakly with $\dot{V}O_2$max: $R = +0·34, p < 0·05$.

Blood oxygen saturation was normal in all patients at rest (91%–97%). In 23 of the 47 patients, ear lobe oxygen saturation fell by 1%–6% from resting state to peak exertion, with rapid recovery to the resting value within two minutes of the end of exercise. In the remaining 24 patients, oxygen saturation did not change significantly. There was no correlation between $\dot{V}E/\dot{V}CO_2$ and change in oxygen saturation.

CONTROLS

Peak oxygen consumption ($\dot{V}O_2$max) ranged from 25 to 93 (median 42) ml/kg/min. Table 3 gives the results of exercise testing and the respiratory variables calculated from the exercise data. $\dot{V}E/\dot{V}CO_2$ at peak exercise ranged from 16·9 to 35·8 (median 25·0). $\dot{V}E/\dot{V}CO_2$ was weakly related to exercise capacity $\dot{V}O_2$max ($r = -0·11, p < 0·0003$). Age and body weight (body mass index) were related to $\dot{V}O_2$max; after adjustment for age and weight by multiple linear regression analysis, the association was only marginally significant ($p = 0·05$).

The ratio $\dot{V}D/\dot{V}E$ at peak exertion was 0·02–0·65, median 0·26. $\dot{V}D/\dot{V}E$ was weakly related to $\dot{V}O_2$max ($r = +0·1, p < 0·001$). Dead space per breath (VD/breath) at peak exertion was 49–1740 ml (median 660 ml). VD/breath was also weakly correlated with $\dot{V}O_2$max ($r = +0·08$, $p < 0·0001$). These relations remained significant after adjustment for age and body weight.

The correlation coefficients between $\dot{V}O_2$max and $\dot{V}E/\dot{V}CO_2$, $\dot{V}D/\dot{V}E$, and VD/breath though statistically significant were only small. In a large scale study it is the magnitude of the association, not the significance, that is clinically relevant. Division of the 1009 controls into deciles of $\dot{V}O_2$max showed that the mean value of $\dot{V}E/\dot{V}CO_2$ was 26·1 in the lowest decile and 24·6 in the highest decile. Similarly, the mean value of $\dot{V}D/\dot{V}E$ was 0·29 in the lowest decile and 0·24 in the highest decile, and VD/breath was 590 ml in the lowest and 680 ml in the highest decile.

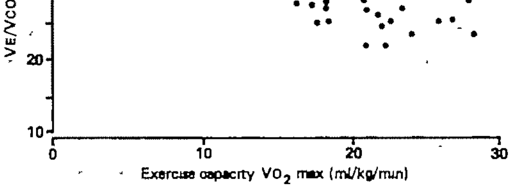

Figure 1 Relation between $\dot{V}E/\dot{V}CO_2$ and $\dot{V}O_2$ max in patients.

OVERALL RELATION BETWEEN $\dot{V}E/\dot{V}CO_2$ AND $\dot{V}O_2$MAX

Figure 2 shows data on the $\dot{V}E/\dot{V}CO_2$ from the controls and from patients with chronic left heart failure. The mean ages of the two groups differ and in the large group of controls the relation of $\dot{V}E/\dot{V}CO_2$ to $\dot{V}O_2$max was adjusted for the effects of age by multiple linear regression analysis. Figure 3 shows the ratio of pulmonary dead space ventilation to total ventilation ($\dot{V}D/\dot{V}E$) and figure 4 shows the total dead space per breath (VD/breath).

Discussion

The mechanisms of dyspnoea and of hyperpnoea in chronic left heart failure are poorly understood. Pulmonary venous hypertension may be the major mechanism causing breathlessness in acute left heart failure, but this does not seem to be the case in chronic heart failure. There is little correlation between pulmonary wedge pressure at rest or during exercise and exercise capacity.[5] Whether exercise is limited by dyspnoea or by fatigue depends upon the type of exercise rather than the peak level of pulmonary wedge pressure attained.[5] When submaximal and maximal exercise tests are performed, both forms of exercise are terminated at similar levels of ventilation,[11] yet if the primary stimulus to excessive ventilation during exercise was an acute increase in pulmonary venous pressure, then the increase in ventilation would be expected to have been greater during the prolonged submaximal test. In both long term and short term drug studies there is often a dissociation between the haemodynamic effects (including changes in pulmonary wedge pressure) and changes in exercise capacity and in dyspnoea.[16–18]

The abnormally increased ventilatory response to exercise in chronic heart failure is well documented; patients with chronic heart failure ventilate more than healthy individuals at the same external work load.[6–8] Exercise hyperpnoea has also been described in patients with severe longstanding mitral stenosis.[19] It has been suggested that the dyspnoea of such patients during exercise might be causally related to this increased ventilation.[11] Several underlying mechanisms have been proposed including the stimulation of chemoreceptors by systemic lactic acidosis,[6 10] the stimulation of muscle metabolic receptors by local skeletal muscle acidosis, the release of carbon dioxide by buffers, altered arterial PCO_2 control, and changes in lung compliance due to congestion and/or chronic fibrosis.[20–22]

Analysis of respiratory gas exchange during exercise has proved useful to examine these hypotheses.[23–26] In healthy individuals during exercise, ventilation is linearly related to the minute production of carbon dioxide.[11] In

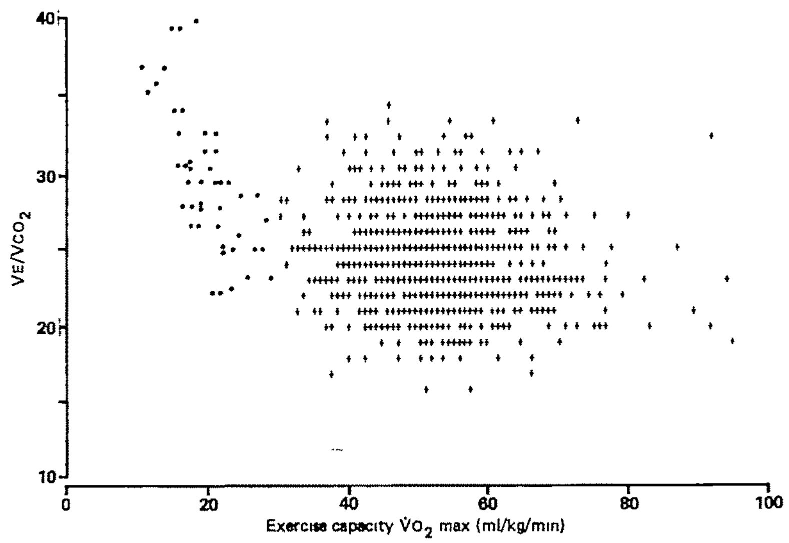

Figure 2 Relation between $\dot{V}$E/$\dot{V}$CO$_2$ and $\dot{V}$O$_2$ max in patients and healthy controls.

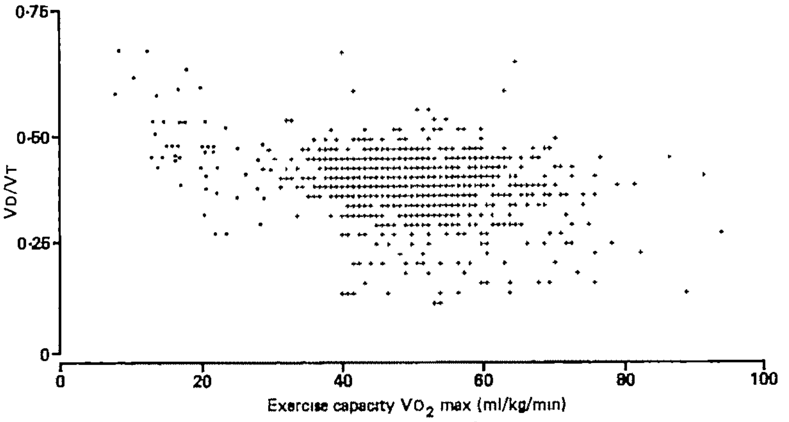

Figure 3 Relation between $\dot{V}$D/$\dot{V}$E and $\dot{V}$O$_2$ max in patients and healthy controls.

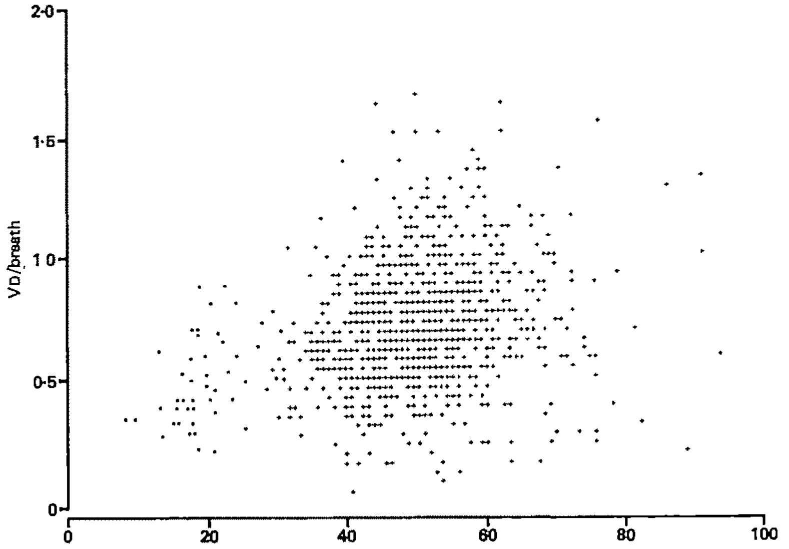

Figure 4 Relation between VD/breath and $\dot{V}$O$_2$ max in patients and healthy controls.

chronic left heart failure the slope of this relation is greatly increased.[20] This suggests that hyperpnoea cannot be solely the result of higher carbon dioxide production, but must involve one of three possibilities. First, excessive ventilation so as to lower mean arterial PCO$_2$, perhaps in response to lactic acidosis; second, increased ventilation of the anatomical dead space by a rapid shallow pattern of breathing; third, increased ventilation of physiological dead space. Analysis of respiratory gas exchange and in particular of $\dot{V}$E/$\dot{V}$CO$_2$ and $\dot{V}$D/$\dot{V}$E allows inferences to be made about gas exchange, dead space, and the matching of ventilation to perfusion.

In the present study we have confirmed previous reports of increased $\dot{V}$E/$\dot{V}$CO$_2$ during exercise.[9 10] End tidal carbon dioxide, corrected by the Jones formula to give an estimate of mean arterial PCO$_2$, is the same in patients with chronic left heart failure and healthy controls, implying normal control of arterial PCO$_2$ in severe heart failure despite abnormal ventilation. Applying the Bohr equation to the data shows that the increase in $\dot{V}$E/$\dot{V}$CO$_2$ represents an increase in the ratio of dead space ventilation to total ventilation ($\dot{V}$D/$\dot{V}$E).

$\dot{V}$D/$\dot{V}$E is higher in the patients with heart failure than in the healthy individuals (table 3). Theoretically this might be because a rapid shallow pattern of breathing increases the proportion of dead space ventilation, but this is not the case because respiratory rate at peak exertion was similar in patients with chronic left heart failure and in healthy individuals. Anatomical dead space is not different in chronic heart failure from normal subjects, and therefore physiological dead space must be increased.

Calculated dead space per breath (VD/breath) varies widely between individuals within both the control group and in patients with chronic heart failure, and there is no significant difference between the groups. This may be because increased $\dot{V}$D/$\dot{V}$E in chronic heart failure is offset by the lower tidal volume at peak exertion (itself the product of a lower peak minute ventilation and normal or slightly raised respiratory rate at peak exertion).

The mechanisms of increased $\dot{V}$E/$\dot{V}$CO$_2$ and $\dot{V}$D/$\dot{V}$E in severe chronic left heart failure have not been elucidated. It has been suggested that chronic pulmonary congestion, damage, and perhaps chronic diffuse fibrosis contribute.[27] Significant correlations between $\dot{V}$E/$\dot{V}$CO$_2$, mean pulmonary artery pressure, and pulmonary vascular resistance were found in one study[28] but not in another study.[29] An alternative explanation is that patients with chronic left heart failure and increased $\dot{V}$E/$\dot{V}$CO$_2$ develop subclinical or even overt pulmonary oedema during exertion. Because oxygen is approximately 20 times less diffusable than is carbon dioxide in a fluid film,[30] a degree of pulmonary oedema sufficient to cause abnormalities in $\dot{V}$E/$\dot{V}$CO$_2$ would be expected to cause proportionately greater abnormalities in oxygen uptake. Important arterial hypoxaemia, however, was not a finding of the present study; furthermore, there was no correlation between the ratio $\dot{V}$E/$\dot{V}$CO$_2$ and the change in oxygen saturation with exercise in individual patients.

The correlation between $\dot{V}$E/$\dot{V}$CO$_2$ and $\dot{V}$O$_2$max in patients with heart failure confirms the reports of Fink *et al*[29] and of Buller and Poole-Wilson.[31] In these studies, however, few patients had a $\dot{V}$O$_2$max of greater than 20 ml/kg/min and so the relation between $\dot{V}$E/$\dot{V}$CO$_2$ and

$\dot{V}O_2$max was not studied over a wide range of $\dot{V}O_2$max. Because end tidal carbon dioxide and arterial P_{CO_2} were not measured, the ratio $\dot{V}_D/\dot{V}_E$ could not be calculated in these studies though it was suggested that physiological dead space was increased.[31]

Regression analysis showed that in patients with chronic heart failure $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_D/\dot{V}_E$ depended strongly on exercise capacity as assessed by $\dot{V}O_2$max. In the controls, however, the relation between $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_D/\dot{V}_E$, and $\dot{V}O_2$max over a wide range of values of $\dot{V}O_2$max was very weak. The difference might simply reflect the difference between health and a disease state. The values of $\dot{V}_E/\dot{V}CO_2$ in patients with mild symptoms of heart failure and reasonable exercise capacity ($\dot{V}O_2$max >20 ml/kg/min) resembled those seen in the controls. There was a point of inflection corresponding to a $\dot{V}O_2$max of approximately 20 ml/kg/min, below which $\dot{V}_E/\dot{V}CO_2$ rises abnormally and the calculated dead space ratio $\dot{V}_D/\dot{V}_E$ increases (figs 2 and 3). This suggests that ventilatory abnormalities develop only when chronic left heart failure exceeds a critical level of severity and exercise capacity falls below $\dot{V}O_2$max of 20 ml/kg/min.

In conclusion, it seems that the increase in $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_D/\dot{V}_E$ in patients with chronic left heart failure is caused by pulmonary ventilation-perfusion mismatching: there are zones which are adequately ventilated or even hyperventilated, yet receive little pulmonary blood flow. At present there is no evidence to indicate whether this occurs on a regional or zonal basis or is distributed at alveolar level throughout the lungs. The threshold of exercise capacity and of severity of heart failure for abnormal increases in $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_D/\dot{V}_E$ could be explained by the existence of a critical level of cardiac output response to exercise, necessary to perfuse adequately all ventilated lung zones.

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Platelet aggregating activity in serum from patients with HLA-B27 associated rheumatic and cardiac disorders: a possible link to the proliferative vascular changes

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Abstract

***Objective*—To search for possible serum factors (immunochemical abnormalities) that reflect HLA-B27 associated inflammatory process with the proliferative endarteritis, which is an important cause of severe bradycardia and aortic valve regurgitation.**

***Patients and methods*—Seventy four men with pacemakers were studied: 24 were HLA-B27 positive and had associated rheumatic and cardiac disorders, 13 were B27 positive but had no clinical or radiographic signs of a related rheumatic condition, and 37 were B27 negative controls. Randomly obtained serum samples were examined for a series of serum factors.**

***Results*—Thirteen (57%) of the 23 patients with HLA-B27 and associated rheumatic and cardiac conditions had platelet aggregating activity in their serum. No such activity was found in sera from patients in the other groups. None the less, immunochemical abnormalities were common among patients of all groups; 30 (41%) had antinuclear antibodies or rheumatoid factor or both.**

***Conclusion*—The platelet aggregating activity found in patients with HLA-B27 and associated rheumatic and cardiac conditions may reflect serum factors that increase the stickiness of platelets and increase their adhesion to the vessel wall. This suggests a link via release of platelet derived growth factor(s) with the characteristic histopathological feature of proliferative endarteritis. Immunochemical abnormalities were common in serum from all men with pacemakers.**

The HLA-B27 allele is associated with a predisposition to seronegative spondarthritides and impairment of the cardiac conduction system,[1-3] the aortic and mitral valves,[4-7] and the myocardium.[8,9] The most common and clinically important cardiac disorders are complete heart block and aortic valve regurgitation. A substantial proportion (15–20%) of men with pacemakers[3,10,11] (but not women[12]) and of white patients with aortic valve regurgitation have the HLA-B27 allele.[13-15] The histopathological features of the disease process include perivascular infiltration of inflammatory cells around small vessels such as the vasa vasorum of the proximal aorta and around vessels in the interventricular septum and vessels adjacent to the affected joints. The lumens of these vessels are obliterated by endothelial and fibromuscular proliferation (endarteritis obliterans).[1,5,16]

In the present study we looked for immunochemical factors in the serum that could be linked to the proliferative vascular disease in HLA-B27 positive patients.

Patients and methods

PATIENTS

We studied men with pacemakers who had been examined for HLA-B27 associated rheumatic disorders.[3,10,11] When the history was taken we noted any signs or symptoms that might have been linked with HLA-B27 such as acute anterior uveitis, low back pain, arthritis or arthralgia, psoriasis, inflammatory bowel disease, and urogenital infection or discharge. The sacroiliac joints in all patients in the three groups had been *x* rayed, and patients with confirmed sacroiliitis were also examined for spondylitis. We used the 1966 New York criteria for ankylosing spondylitis and sacroiliitis was diagnosed only when we found radiographic changes of grade 2 (definite changes) to 4.[17] The patients' HLA type was determined by a standard microlymphocytotoxicity test.[18]

Group 1—We studied 24 HLA-B27 positive men (mean age 74 years, range 36–91) with rheumatic and cardiac syndromes. Ankylosing spondylitis was present in 14 patients (five also had had uveitis). Five patients had sacroiliitis or typical spondylitis (two with uveitis). In five patients peripheral arthritis and/or uveitis dominated. Twenty patients had a pacemaker because of second and third degree atrioventricular block. Four patients had other bradycardias, mainly sinus node disease with or without supraventricular tachycardias. Thirteen patients had regurgitant aortic valves, which in three had been replaced. Four patients had a history of myocardial infarction.

Group 2 consisted of 13 HLA-B27 positive men (mean age 79, range 59–90) with complete heart block but without any clinical or radiographic evidence of a rheumatic disorder.

Group 3 was the control group of 37 men (mean age 76, range 39–91) with complete heart block. They were all HLA-B27 negative and had no radiographic signs of sacroiliitis.

BLOOD TESTS

We collected blood samples when the patients came for routine examination of their pacemaker systems. Blood was drawn at room temperature. Blood for cryoglobulin determination was immediately transferred to a centrifuge and the serum was separated at 37°C. Serum samples were stored at −70°C.

ANALYTICAL METHODS

C reactive protein, orosomucoid, antichymotrypsin, and complement factors C3 and C4 were measured by the Laurell rocket electrophoresis technique.[19] IgG, IgA, and IgM concentrations were measured on commercial immunodiffusion plates (Behringewerke, Marburg, Germany). Complement activation via the classical and alternative pathways was assessed by haemolysis-in-gel methods.[20] Rheumatoid factor was detected by the Waaler-Rose test. Antinuclear antibodies, antimitochondrial antibodies, and smooth muscle antibodies were measured by a standard indirect immunofluorescent technique. In patients with antinuclear antibodies we used the *Crithidia lucilliae* method to detect anti-DNA antibodies. Antibodies to extractable nuclear antigens were analysed by counter immunoelectrophoresis.[21]

Circulating soluble immune complexes were assayed by a solid phase C1q-binding enzyme linked immunoadsorbent assay (ELISA),[22] and a solid phase conglutinin binding ELISA.[23] We used Myllylä's platelet aggregation test.[24] A titre $\geqslant 1/8$ was regarded as abnormal; though 99 of 100 healthy blood donors had a titre $\leqslant 1/4$.[25]

STATISTICAL ANALYSIS

We used Fisher's exact test to determine the statistical significance of differences between groups.

The study was approved by the Medical Ethics Committee of the Karolinska Institute and the patients gave their informed consent.

Results

The platelet aggregation test was positive in 13 (57%) out of 23 of the patients in group 1, though two had a titre 1/4 that is occasionally seen in healthy controls. None of the patients in groups 2 and 3 had a positive platelet aggregation test (group 1 *v* group 2, $p < 0{\cdot}001$; group 1 *v* group 3, $p < 0{\cdot}001$). All five of the 13 patients with a positive platelet aggregation test with titres $> 1/4096$ had aortic regurgitation.

Serum from six (26%) of the group 1 patients contained cryoglobulins. None of the patients in the other groups was positive (group 1 *v* group 2, $p \leqslant 0{\cdot}05$; group 1 *v* group 3, $p < 0{\cdot}01$).

The assay for C1q was positive in one patient in group 1 and in two patients in group 2. The conglutinin test was positive in two patients in group 1 but not in any patients in groups 2 and 3.

Serological signs of inflammatory activity, such as increases in sedimentation rate and other acute phase reactants including C3 and C4, were common in all groups (table). But there were no clear cut differences between the three groups or any association between the presence of platelet aggregating activity and an increase in acute phase reactants.

We found autoantibodies in 31 of the 74 patients. Rheumatoid factor, mostly in low titre, was found in all groups: in seven (29%) of 24 in group 1, in one out of 13 in group 2, and in seven (19%) of 37 in group 3. Antinuclear antibodies were present in four (17%) (all $\leqslant 1/25$) of 24 in group 1, in three (23%) (two $\geqslant 1/100$) of 13 in group 2, and in 12 (32%) (7 $\geqslant 1/100$) of 37 in group 3. Though antinuclear antibodies were more common and were found in much higher titres in group 3 than in group 1, the difference was not significant. We did not find DNA antibodies or antibodies directed against extractable nuclear antigens in any patient. A patient with chronic

Results of blood tests in the three groups of patients with pacemakers

Variable	*Group 1* *(n = 24)* *B27+/RS+*	*Group 2* *(n = 13)* *B27+/RS−*	*Group 3* *(n = 37)* *B27−/RS−*	*p*
ESR > 15 mm/h	9/20	6/11	8/29	NS
Leucocytes > 9·0 × 10^9/l	4/21	3/11	4/33	NS
Abnormal differential count*	5/21 (3)	4/12 (2)	9/31 (4)	NS
CRP ⩾ 0·01 mg/ml	6/24	1/13	3/19	NS
Orosomucoid ⩾ 1·0	4/24	3/13	6/37	NS
Antichymotrypsin	4/24	2/13	4/37	NS
C3 (increased)	4/24	0/13	1/37	NS
C4 (increased)	5/24	0/13	3/37	NS
RF	7/24	1/13	7/37	NS
ANA	4/24	3/13	12/37	NS
Mitochondrial antibodies	0/23	0/13	1/37	
Smooth muscle antibodies	0/23	0/13	3/37	
Cryoglobulins	6/23	0/13	0/36	1 *v* 2: ⩽ 0·05 1 *v* 3: < 0·01
C1q-ELISA	1/23	2/13	0/35	
Conglutinin	2/23	0/13	0/35	
PLA	13/23	0/13	0/37	1 *v* 2: < 0·001 1 *v* 3: < 0·0001

Fisher's exact test was used.
*Figures in parentheses are eosinophils
ANA, antinuclear antibodies; C, complement factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PLA, platelet aggregation test; RF, rheumatoid factor.

liver disease in group 3 had mitochondrial antibodies (titre $\geqslant 1/1600$).

Discussion

Since 1973 when the association between HLA-B27 and ankylosing spondylitis was reported,[26 27] a link has been sought between HLA-B27 and the histopathological features and clinical characteristics of the HLA-B27 associated rheumatic disorders.

Our results were unremarkable and consistent with other studies of patients with ankylosing spondylitis. There are, however, three observations of interest. First, we found platelet aggregating activity in 57% of the patients with HLA-B27 associated disorders (group 1) but not in the other groups. This is an original observation. We used platelet aggregating activity to search for circulating immune complexes. Norberg found platelet aggregating activity in 36 out of 171 patients with rheumatoid arthritis.[28] This activity was probably due to the presence of circulating immune complexes.[28] In our study, however, only three patients with the rheumatic and cardiac syndromes had positive C1q-binding or conglutinin tests, suggesting circulating immune complexes, and two of them had no platelet aggregation. Furthermore, platelet aggregating activity was not associated with an increase in acute phase reactants, which were normal in eight of the 13 patients with platelet aggregating activity. Neither was there a relation with increased immunoglobulin concentrations, which were found in only two of the 24 patients in this group.

Our observations need to be confirmed by other in vitro and in vivo tests of platelet aggregation and the cause of this activity must be elucidated. In theory, the platelet aggregating activity could be related to serum factors that can increase the stickiness of platelets and facilitate their adhesion to the vessel wall.[29] Platelet derived growth factor locally released by activated or damaged platelets may be involved in the intimal proliferation that has been found in patients with HLA-B27 associated disease.[1 5 7 16] A similar process may lead to vascular proliferative lesions in different diseases.[30]

Serum samples from six of the HLA-B27 positive patients with rheumatic and cardiac disease also contained cryoglobulins. Mixed cryoglobulins are commonly encountered in various types of vasculitic disorders,[31] but none of our patients had clinical or immunological signs supporting a diagnosis of systemic lupus erythematosus or other autoimmune diseases. Two patients with cryoglobulins gave a history of Raynaud-like symptoms, however.

We found that immunochemical abnormalities were common in all groups. This accords with a recent report of antinuclear antibodies in 54% of 65 patients with atrioventricular block and in 47% of 45 patients with sick sinus syndrome, all of them with pacemakers.[32]

We based the diagnosis of rheumatoid disease in patients with the HLA-B27 allele on the presence of one or more of the most typical clinical manifestations: radiographically verified sacroiliitis, Reiter's disease, and acute anterior uveitis. We grouped the HLA-B27 associated syndromes together because of (*a*) the considerable clinical overlap in individuals and within families; (*b*) the various disease manifestations or tissue disorders show separate association with HLA-B27[33–35]; (*c*) the similarity of the heart manifestations in patients with different B27 associated rheumatic and ocular disorders, and the fact that in white men *the combination* of clinically significant bradycardia and pure aortic valve regurgitation is basically an HLA-B27 associated syndrome with 88% of the patients being HLA-B27 positive[3 15]; (*d*), and histopathological changes are similar in periarticular and non-articular tissues.[5 16] None the less, the HLA-B27 allele is not a diagnostic criterion in the disorders listed above, and disease processes not associated with HLA-B27 may lead to similar clinical manifestations. All the patients in group 1 had the rheumatic and/or ocular manifestations associated with HLA-B27. Six of seven patients with rheumatoid factor in group 1 had radiographically confirmed sacroiliitis or spondylitis or both. The seventh patient had a titre 1/20. Furthermore, other criteria of rheumatoid arthritis were not found in these patients. We therefore firmly believe the rheumatoid factor was coincidental. Presumably the disease process associated with HLA-B27 was also the underlying cause of the cardiac disease in these patients. No other cause was found, and there was histopathological evidence to support this assumption in three patients.[7]

We cannot regard the presence of cardiac disorders as evidence of a particularly severe inflammatory process in our patients because the severity of joint disease does not parallel the cardiac manifestations.[3 15] Furthermore, because up to 20% of patients with ankylosing spondylitis have either high degree atrioventricular block or aortic regurgitation,[36 37] earlier studies of immunochemical serum factors must surely have included patients with these cardiac manifestations.

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Double blind crossover comparison of the effects of dual chamber pacing (DDD) and ventricular rate adaptive (VVIR) pacing on neuroendocrine variables, exercise performance, and symptoms in complete heart block

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Abstract

***Objective*—To compare the effects of dual chamber pacing (DDD) and ventricular rate adaptive pacing (activity sensing) (VVIR) in patients with complete heart block.**

***Design*—Double blind crossover comparison with one month in each pacing mode.**

***Patients*—10 consecutive patients aged 23–74 presenting with complete anterograde atrioventricular block at rest and on exercise and with an intact atrial rate response received Synergyst I (Medtronic) pacemakers.**

***Main outcome measures*—Symptom scores, maximal exercise performance on a treadmill, and the plasma concentrations of atrial natriuretic peptide, adrenaline, and noradrenaline.**

***Results*—No significant differences were identified between pacing modes in symptom scores for dyspnoea, fatigue, and mood disturbance; exercise time; and maximal oxygen consumption. One patient with intact ventriculoatrial conduction developed pacemaker syndrome during VVIR pacing. Resting plasma concentrations of atrial natriuretic peptide were raised in complete heart block and were restored to normal by DDD pacing but not by VVIR pacing. Resting plasma catecholamine concentrations were normal in complete heart block and in both pacing modes. During exercise the increase in the concentrations of all three hormones was similar in both pacing modes.**

***Conclusions*—In patients with complete anterograde and retrograde atrioventricular block, symptoms and maximal exercise performance were no better during DDD than during VVIR pacing.**

In most patients who need permanent pacemakers, symptoms and exercise performance are better with rate responsive pacing than with fixed rate ventricular pacing. This has been shown in comparisons with dual chamber (DDD) pacing[1–3] and also with various sensor-driven single chamber ventricular rate responsive (VVIR) systems.[4–6] However, it is not clear whether either of these rate responsive modes is better than the other. Because the Synergyst I (Medtronic) pacemaker can operate in the DDD and activity sensing VVIR pacing modes we were able to compare the effects of these two modes in the same patient.

Patients and methods

The study was designed as a double blind prospective crossover comparison of the effects of DDD and VVIR pacing on symptoms, maximal exercise capacity, and plasma concentrations of adrenaline, noradrenaline, and atrial natriuretic peptide in complete heart block. It was approved by the ethics committee of Glasgow Royal Infirmary and all patients gave written informed consent before entry. There were seven men and three women (mean age 56 years (range 23–74)). The underlying cardiac diagnoses were ischaemic heart disease (two), hypertension (two), congenital heart block (two), and idiopathic fibrosis of the conducting tissue (four). Only two patients were receiving cardiovascular drugs and treatment was not changed during the course of the study. The mean ejection fraction was 58% (range 40–74) and none of the patients had any clinical evidence of cardiac failure.

STUDY PROTOCOL

We implanted a Synergyst I (Medtronic) pacemaker in 10 consecutive patients presenting with complete anterograde atrioventricular block at rest who were capable of completing an exercise protocol. We excluded patients with recent myocardial infarction, appreciable angina or respiratory disease, chronic atrial flutter/fibrillation, and exercise induced arrhythmias.

Patients performed exercise tests before permanent pacing to confirm an intact atrial rate response, before randomisation to facilitate programming of rate response in the VVIR mode, and after each treatment period. The preliminary tests also served to familiarise patients with the exercise apparatus. Program settings were chosen with the aim of allowing similar maximum ventricular rates in both modes. Patients were then randomised to either the DDD or VVIR mode for one month at the end of which they crossed over to the opposite mode for a further month. Peripheral venous blood samples were taken from indwelling cannulas at rest before implantation of the pacemaker, and at rest and after exercise after each one month period. Symptom questionnaires were also completed at each visit. All pacemaker programming and electrocardiographic monitoring during exercise testing was performed by one operator (CW). All of the exercise tests were supervised by a different observer (RC) who was not aware of the pacing mode and was screened from the electrocardiographic monitor during testing.

SYMPTOM SCORES

Symptoms were assessed at the end of each one month period by a self administered questionnaire. This questionnaire was developed at McMaster University and has been used in a previous study to compare different pacing modes.[4] Three sets of eight questions related to dyspnoea, fatigue, and mood disturbance were answered by marking an ungraduated 100 mm linear visual analogue scale cued with "very much" and "not at all". The distances of all the marks for each category of questions were summed: a maximum score of 800 was possible.

EXERCISE PROTOCOL

Maximal symptom limited treadmill exercise tests with concurrent measurement of respiratory gas exchange were used. In our laboratory the limb of the breathing circuit for inspiration is fitted with a turbine ventilometer and the limb for expiration includes a mixing chamber from which mixed expiratory gases are measured by polarographic oxygen and infrared carbon analysers. The output of the ventilometer and gas analysers are processed by an on line microcomputer (PK Morgan Exercise Test System) to allow continuous measurement of gas exchange and inspired minute ventilation. For the exercise protocol patients were monitored at rest for two minutes to establish a steady state, then they performed incremental treadmill exercise at a fixed gradient of 10 degrees starting at one mile per hour and increasing by 0·5 miles per hour every minute. Maximal oxygen consumption[7] and the respiratory anaerobic threshold[8] were determined by standard criteria. We used a fixed gradient because activity sensing pacemakers respond to increases in treadmill speed rather than incline.[5 9]

EJECTION FRACTION

This was calculated from cross sectional echocardiographic images obtained in DDD mode. We used an area × length formula.

ASSAYS

Atrial natriuretic peptide was measured by radioimmunoassay[10] (normal range 5–50 pg/ml). Catecholamines were measured by radioenzymatic assay[11] (normal values adrenaline < 1·0 nmol/l and noradrenaline < 5·0 nmol/l).

STATISTICAL ANALYSIS

To assess the distribution of the data derived from this study we calculated the standardised skewness and kurtosis of each of the variables. Normally distributed values were expressed as mean (SEM) and skewed values as the median (interquartile range). Paired two tailed group comparisons were made with Student's *t* (parametric) or Wilcoxon signed rank (nonparametric) tests as appropriate. p Values of < 0·05 were regarded as significant.

Results

SYMPTOMS

Only one patient requested early crossover

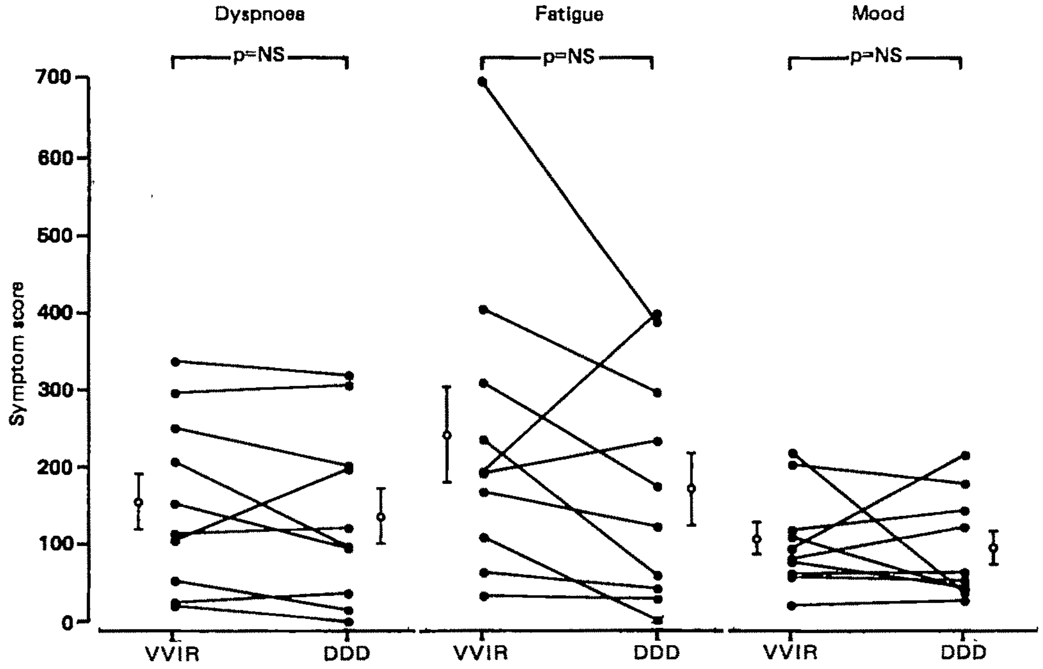


Figure 1 Individual values and means (SEM) of symptom scores during VVIR (ventricular rate adaptive pacing) and DDD (dual chamber pacing).

Table 1 Results (mean (SEM)) of maximal symptom limited cardiopulmonary exercise testing

Variable	*VVIR*	*DDD*
Exercise time (s)	477 (32)	489 (31)
Maximal oxygen consumption (ml/min/kg)	22·9 (1·4)	22·1 (1·2)
Peak ventilation (l/min)	62·7 (5·4)	58·4 (6·0)
Oxygen consumption at anaerobic threshold (ml/min/kg)	16·7 (0·9)	16·8 (0·9)
Maximal carbon dioxide production (ml/min/kg)	24·8 (1·8)	23·0 (1·4)
Basal respiratory quotient	0·84 (0·03)	0·86 (0·04)
Peak respiratory quotient	1·06 (0·05)	1·06 (0·05)

VVIR, ventricular rate adaptive pacing, DDD, dual chamber pacing.

from VVIR back to DDD for symptoms consistent with pacemaker syndrome. This was the only patient with evidence of intact ventriculoatrial (VA) conduction. Nine patients expressed no overall preference for either pacing mode. In keeping with this, there were no significant differences in any of the three symptom scores between VVIR and DDD pacing (fig 1).

EXERCISE PERFORMANCE (TABLE 1)

Though the program settings were aimed at allowing a similar maximum heart rate in both pacing modes, the maximum heart rate achieved was significantly higher in the DDD mode than in the VVIR mode: 136 (4) *v* 117 (3) (fig 2). Seven of the 10 patients actually reached their programmed upper tracking rate during exercise in DDD mode and reverted to a Wenckebach pattern of atrioventricular conduction. In six this upper tracking rate was 144 beats per minute. There was no significant difference between the modes in exercise time (fig 2), maximal oxygen consumption, or peak ventilation (fig 3). Oxygen consumption at anaerobic threshold, maximal carbon dioxide production, and the mean resting and peak respiratory quotients were also similar in both modes. The resting values were close to the expected normal values of around 0·85, indicating that a reasonable steady state of respiratory gas exchange had been achieved.

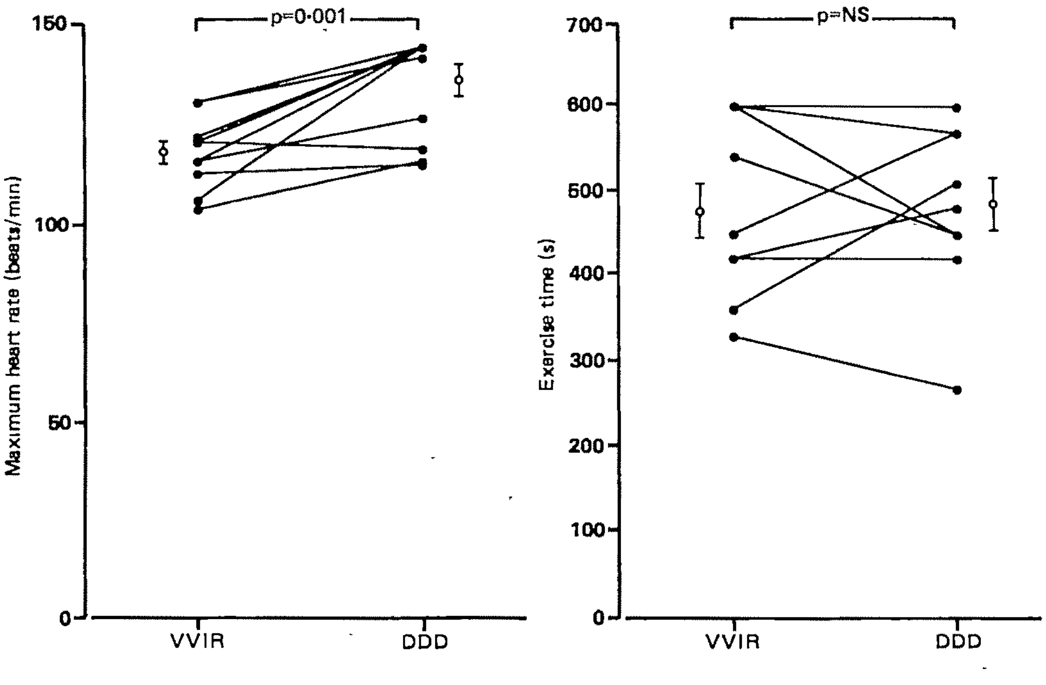
ATRIAL NATRIURETIC PEPTIDE (TABLE 2)

Before pacemaker implantation seven patients had resting values above the normal range. After one month of DDD pacing only two patients continued to have raised concentrations of atrial natriuretic peptide and there was a significant fall in the median concentration. No such fall occurred after VVIR pacing; five patients continued to have values above the normal range. Exercise produced significant rises in concentration of atrial natriuretic peptide in both pacing modes. Although the median concentration on exercise was higher in VVIR than DDD with 7/10 *v* 4/10 subjects reaching concentrations above the normal range, the difference between the modes just failed to reach statistical significance (exact p value = 0·05). There was no difference between pacing modes in either the absolute or percentage increase in atrial natriuretic peptide on exercise. The patient with pacemaker syndrome during VVIR pacing had raised plasma atrial natriuretic peptide at rest with a substantial rise to 196 pg/ml on exercise. In DDD mode his atrial natriuretic peptide concentration was normal at rest and remained within the normal range on exercise.

CATECHOLAMINES (TABLE 2)

Before pacemaker implantation one patient had a slightly raised plasma concentration of noradrenaline at rest (5·3 nmol/l), but otherwise both adrenaline and noradrenaline concentrations were normal. Resting concentrations were all within normal limits in both pacing modes and there was no difference between modes in either the resting or exercise concentrations of adrenaline or noradrenaline. Though there was an overall increase in the concentration of both catecholamines on exercise in both modes, there was no difference between modes in either the absolute or percentage increases.

Figure 2 Individual values and means (SEM) of maximum heart rate and exercise time on treadmill exercise testing during VVIR and DDD pacing.



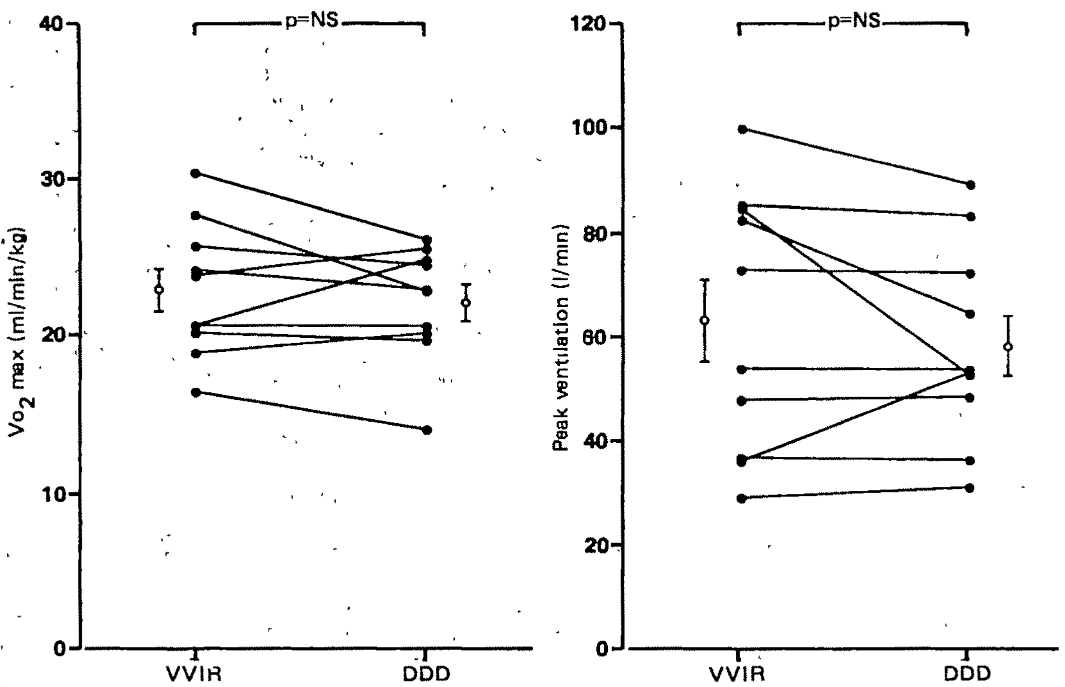


Figure 3 Individual values and means (SEM) of maximal oxygen consumption and ventilation on treadmill exercise testing during VVIR and DDD pacing.

Discussion

The contribution to cardiac output of a properly timed atrial contraction diminishes with increasing heart rate[12 13] and filling pressures.[14] There were no significant differences in exercise capacity in earlier short term crossover studies of patients paced at a fixed ventricular rate similar to that achieved on exercise during atrioventricular synchronous pacing.[15 16] In the present within patient comparative study the addition of atrioventricular synchrony produced no advantage over the provision of rate response alone. Physiologically the PR interval gradually shortens during exercise as heart rate rises, but studies attempting to show that such atrioventricular interval hysteresis improves exercise performance during DDD pacing have produced both positive[17 18] and negative results.[19 20] In view of this, we did not attempt to "optimise" the programmed atrioventricular interval. To maintain a 1:1 atrioventricular relation at high paced ventricular rates without atrioventricular interval hysteresis, it is necessary to shorten either the programmed atrioventricular interval or the post-ventricular atrial refractory period. But these manoeuvres reduce the time for atrial filling and predispose the patient to pacemaker mediated tachycardia respectively.

A limitation to the wider application of VVIR pacing is the problem of pacemaker syndrome, which was seen in one patient in this series. This prevalence of intact ventriculoatrial conduction is identical to that found in a similar study by Lipkin *et al.*[4] Temporal variability in the integrity of ventriculoatrial conduction weakens the relevance of any single pre-implantation assessment but it is known that the incidence of intact ventriculoatrial conduction is much higher in certain patient groups. Thus in sick sinus syndrome it is accepted that VVI pacing produces an unacceptably high incidence of pacemaker syndrome and that atrial or dual chamber pacing, which avoids this problem, is preferable.[21] However, in patients with complete anterograde and retrograde heart block DDD pacing seems to confer no benefit over VVIR in terms of symptoms or exercise performance.

Asynchronous atrial contraction, as occurs in complete heart block, raises intra-atrial pressure and stimulates the release of atrial natriuretic peptide.[22] We found raised concentrations in most of our patients before pacemaker implantation. Dual chamber pacing in complete heart block restores atrial natriuretic peptide concentrations to normal in most patients and this has been offered as evidence of the physiological nature of this mode.[22] By contrast, VVIR pacing did not

Table 2 Neuroendocrine variables (median (interquartile range)) in study patients

		VVIR			*DDD*		
	Pre-implant	*Rest*	*Exercise*	*Change on exercise (%)*	*Rest*	*Exercise*	*Change on exercise (%)*
Atrial natriuretic peptide (pg/ml)	66 (38–80)	52 (20–73)	114* (38–196)	61 (38–168)	20† (15–33)	40* (18–76)	76 (39–125)
Adrenaline (nmol/l)	0·20 (0·10–0·35)	0·10 (0·07–0·40)	0·40 (0·20–0·70)	186 (0–400)	0·09 (0·06–0·25)	0·75* (0·40–1·45)	566 (193–1025)
Noradrenaline (nmol/l)	1·4 (0·8–2·6)	1·5 (0·3–3·0)	4·2 (0·5–7·0)	50 (0–204)	2·0 (1·8–2·4)	10·7* (4·7–12·2)	366 (123–453)

*$p < 0.05$ *v* resting value; †$p < 0.05$ *v* pre-implant and VVIR values.

restore normal concentrations. It has previously been shown that atrial natriuretic peptide concentrations rise on exercise[23 24] and during ventriculoatrial pacing.[25] By providing higher ventricular rates on exercise, VVIR pacing increases the frequency of asynchronous atrial contraction, which may result in an augmented rise in atrial natriuretic peptide on exercise even in the absence of intact ventriculoatrial conduction. We did find a trend towards higher concentrations on exercise in the VVIR mode than in the DDD mode (exact p value = 0·05), but there was no difference between modes in either the absolute or percentage change on exercise. As in published reports, our only patient with pacemaker syndrome during VVIR pacing had very high plasma concentrations of atrial natriuretic peptide.[26] However, the relevance of this finding to the vasomotor changes and symptoms of pacemaker syndrome remains unclear.[24]

In patients with impaired ventricular function cardiac release of noradrenaline on exercise is higher during VVI pacing than during atrial synchronous pacing.[27] This accounts for the much greater increases in stroke volume on exercise seen in VVI mode and partly offsets the lack of a rate response.[28] Though we only measured peripheral venous catecholamine concentrations, our results suggest that VVIR pacing is not associated with undue activation of the sympathetic nervous system either at rest or on exercise.

Single chamber ventricular pacemakers are easier and cheaper to implant than DDD systems and they avoid the problems of atrial lead displacement, atrial malsensing, and cross-talk. They can continue to provide rate response if atrial fibrillation or chronotropic incompetence develop. A potential disadvantage of VVIR pacing is the possible increased incidence of the development of atrial fibrillation with its attendant risk of thromboembolism. However, though this has been shown to be relevant in patients with sinus node disease,[29 30] in theory it is less of a problem in patients with retrograde atrioventricular block. Our data indicate that it would be appropriate to consider VVIR activity sensing pacemakers or other single chamber rate-variable systems to provide rate response in patients with complete anterograde and retrograde heart block and preserved ventricular function. Furthermore, it may not be necessary to have a policy of repeatedly exercising and reprogramming these patients in an attempt to obtain the maximum rate response out of the system. Indeed, perhaps the most interesting finding of this study is that despite a lower maximum heart rate in VVIR mode, comparable levels of symptoms and exercise performance to DDD pacing were achieved with only one or in some cases no adjustment to the nominal program settings. It may be that adaptive mechanisms permit the maintenance of tissue oxygen delivery during VVIR pacing despite lower heart rates. These mechanisms remain speculative but could involve neuroendocrine mediated alterations in cardiac loading and/or contractile function leading to increases in stroke volume. In the minority of patients with complete heart block and intact ventriculoatrial conduction it is probably better to avoid the risk of pacemaker syndrome by establishing atrial synchronous ventricular pacing. It remains to be determined whether other groups such as older patients and those with angina, significantly impaired ventricular function, and/or overt cardiac failure benefit from DDD pacing.

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PLANTS IN CARDIOLOGY

Filipendula ulmaria (L.) Maxim meadowsweet or queen of the meadow; and *Salix alba* L., white willow. From Gerard J. *The Herball or generall historie of plantes.* 2nd ed. London. Thomas Johnson, 1633.

Aspirin

The success of quinine from 1630 onwards in treating malaria led to its use in other febrile conditions. So when the Reverend Edward Stone in 1763 noticed that powdered bark of the willow tree, *Salix* species (Salicaceae), had a bitter taste like quinine he used it as a substitute for the expensive imported cinchona bark. Its active principle—salicin, which is converted into salicylic acid in the body—was isolated in 1830 and introduced for the treatment of acute rheumatic fever by Dr Thomas Maclagan of Dundee in 1876. He used it in the erroneous belief, based on the Doctrine of Signatures, that because the disease was prevalent in cold damp localities *Salix*, a typical marsh plant, would be nature's remedy. None the less, he got the right answer.

Salicylic acid was originally produced in 1835 from salicylaldehyde found in *Spiraea ulmaria*, now *Filipendula ulmaria* (Rosaceae), the meadowsweet. It became freely available only with the development of a synthetic process in 1874. Its use as an "internal antiseptic" in typhoid fever revealed its antipyretic property. This, together with Maclagan's work, led to its use in rheumatic fever and other rheumatic diseases.

After gastric irritation prevented his father from taking sodium salicylate to treat his chronic arthritis Felix Hoffman, a chemist with the Bayer Company, produced acetylsalicylic acid in 1899 (it had been synthesised elsewhere in 1853). He gave it the trade name Aspirin (*a* for acetyl; *spir* for spiraea; and *in*, a common ending for drugs). This is now the generic name.

The family Salicaceae consists mainly of trees and shrubs from the northern temperate region and has only three genera. The Rosaceae are more numerous (over 100 genera and 3000 species) and more widely distributed. They vary from trees to herbs and include apples, plums, and strawberries. Some of the Rosaceae species yield vitamin C but otherwise neither the Rosaceae nor the Salicaceae contain other important medicines.

A HOLLMAN

Br Heart J 1991;65:194–200

Diastolic disease in left ventricular hypertrophy: comparison of M mode and Doppler echocardiography for the assessment of rapid ventricular filling

C H Lee, J C Hogan, D G Gibson

Abstract

***Objective*—To investigate possible discrepancies between M mode and Doppler echocardiography in assessing early diastolic filling.**

***Design*—Forty seven patients with left ventricular hypertrophy due to aortic stenosis and 26 healthy controls with a similar age range were studied by M mode, Doppler, apexcardiography, and phonocardiography. The patients also underwent cardiac catheterisation. M mode echograms were digitised by a computer. Early diastolic filling in both groups as assessed by the two techniques was compared.**

***Setting*—A tertiary cardiac referral centre with facilities for non-invasive and invasive investigations.**

***Subjects*—Patients referred for assessment of aortic stenosis who had left ventricular hypertrophy.**

***Main outcome measures*—Filling velocities on Doppler and rates of wall thinning and dimension increase on M mode.**

***Results*—Digitised M mode indices of diastolic filling (peak wall thinning rate 6·4 (3·0) *v* 10·0 (3·0) cm/s and peak rate of dimension increase 9·3 (3·3) *v* 16 (4·5) cm/s) in the patients and controls were consistently different. In contrast, the Doppler A/E ratio and peak E wave velocity were not; they varied widely among patients with left ventricular hypertrophy. In part, this variability was because the Doppler A/E ratio, but not the digitised M mode indices, was very sensitive to the abnormalities of isovolumic relaxation frequently present in left ventricular hypertrophy. The Doppler A/E ratio varied similarly with age in both normal and hypertrophied hearts; in the patients with ventricular hypertrophy the peak rate of dimension increase depended on age only, whereas the thinning rate was independent of age in both the patients and controls. Neither the A/E ratio nor the M mode indices could be related to the left ventricular end diastolic pressure or the peak aortic pressure difference.**

***Conclusions*—When Doppler and M mode techniques are used to assess rapid filling in patients with left ventricular hypertrophy the M mode indices are more consistently abnormal. The two methods measure different aspects of left ventricular diastolic function and should be regarded as complementary rather than interchangeable.**

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All phases of diastole can be abnormal in left ventricular hypertrophy. Particularly prominent is a reduced rate of rapid early diastolic filling, which has been assessed both by Doppler and digitised M mode techniques.[1 2] Because the physical basis of these techniques is different the information they give may not be the same, particularly as a recent comparison during isovolumic relaxation found major discrepancies between the two techniques.[3] We therefore examined possible differences in their performance in assessing rapid filling in a homogeneous group of patients with left ventricular hypertrophy due to aortic stenosis and compared the results with those from healthy controls of a similar age range.

Patients and methods

STUDY POPULATION

We studied 47 patients (24 men, 23 women, age 14–82) with left ventricular hypertrophy (end diastolic posterior wall thickness greater than 1·1 cm). All had clinical and investigative evidence of important aortic stenosis and were being considered for aortic valve replacement. Cardiac catheterisation and coronary angiography were undertaken as part of the preoperative assessment. All patients were in sinus rhythm and none had a dilated left ventricle (end diastolic dimension > 6 cm). Twenty six healthy controls (18 men, eight women, age 20–82) underwent similar non-invasive examinations.

M MODE ECHOCARDIOGRAPHY

M mode echograms of the mitral valve and left ventricle were recorded with a 3·0 MHz transducer and ATL Imager Mk 300I equipment. The left parasternal long axis view was used with the patient in the left lateral position. Phonocardiograms and electrocardiograms

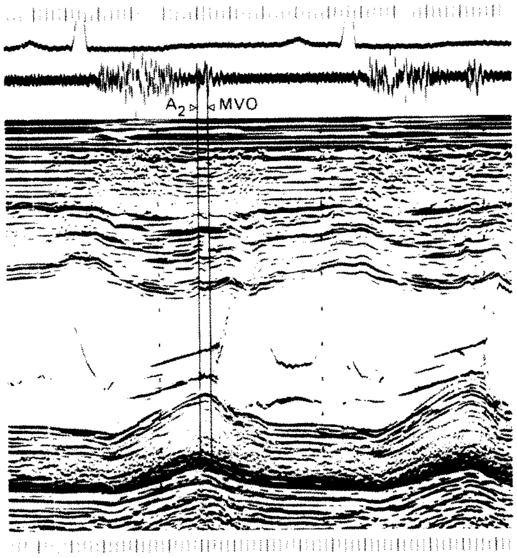

Figure 1 M mode echogram of the left ventricle from a patient with left ventricular hypertrophy secondary to aortic stenosis, showing aortic valve closure (A_2) on the phonocardiogram and mitral cusp separation (MVO) on the M mode.

were recorded simultaneously by a Honeywell recorder at a paper speed of 10 cm/s. Only records showing clearly the point of mitral cusp separation and continuous echoes from both the septum and posterior wall were used for analysis (fig 1). Aortic valve closure (A_2) was taken as the onset of the first high frequency vibration of the second heart sound recorded on the phonocardiogram and was checked with the aortic echograms and the aortic closure artefact on Doppler recordings. The isovolumic relaxation time was measured as the interval from A_2 to the initial separation of the mitral cusps. The thickness of the septum and posterior wall and the left ventricular internal dimension were measured at end diastole. The radius to thickness ratio was obtained by dividing half the left ventricular dimension by the average wall thickness.[4]

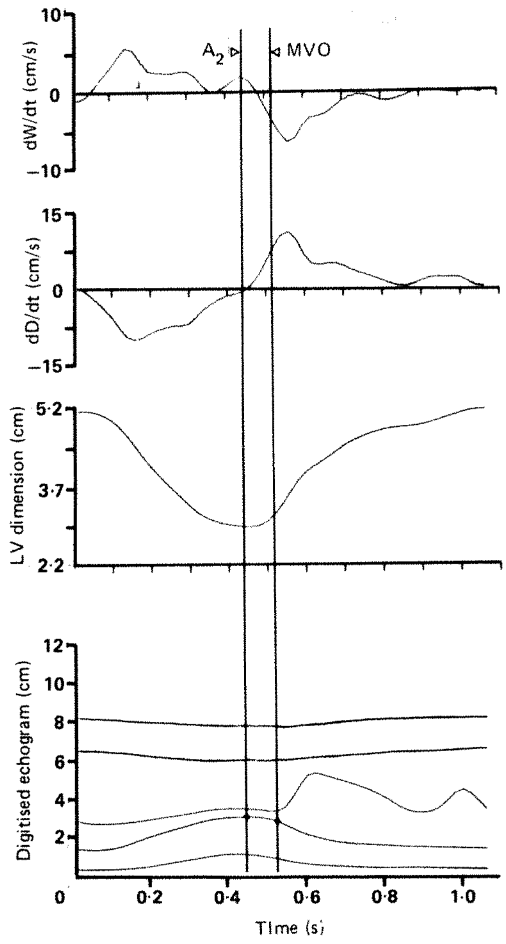

Figure 2 Digitised M mode echocardiogram showing the original digitised echogram, and plots of left ventricular dimension, rate of change in dimension (dD/dt), and rate of change in wall thickness (dW/dt). The two vertical lines correspond to the time of aortic valve closure (A_2) and mitral cusp separation (MVO).

Echocardiograms were digitised[5] and the peak rates of posterior wall thinning during left ventricular relaxation (dW/dt) and the increase in left ventricular dimension (dD/dt) determined. The intervals from A_2 to peak dD/dt and from minimum cavity dimension to mitral valve opening were measured and the increase in transverse cavity dimension during that period expressed as a percentage of the total dimension change during the cardiac cycle (fig 2).

An approximation to left ventricular mass was calculated from the equation[6]:

$$\text{LV mass} = 1{\cdot}05\ ([\text{LVEDD} + \text{PW} + \text{IVS}]^3 - \text{LVEDD}^3) - 14 \text{ grams}$$

where LVEDD is the left ventricular end diastolic dimension (cm) and PW and IVS are the posterior wall and septal thickness in end diastole (cm), respectively. We used the leading edge for all measurements.

DOPPLER ECHOCARDIOGRAPHY

Doppler recordings were made with Doptek equipment and a 2·0 MHz transducer. Forward transmitral flow was recorded in all patients. Peak mitral flow velocity was initially identified by continuous wave Doppler and then recorded with pulsed mode and a 3 mm gate. A wall filter of 250 Hz was used in all cases. Records were taken at a paper speed of 10 cm/s, again with simultaneous phonocardiograms and electrocardiograms. The peak velocities of the atrial (A) wave and the early (E) wave were recorded and their ratio (A/E ratio) derived. The intervals from A_2 to peak transmitral flow velocity and A_2 to peak dD/dt were measured and the phase lag between the two determined.[7] The peak instantaneous pressure difference across the aortic valve was determined in all patients by continuous wave Doppler from the apical position. Mean values from three cardiac cycles were used in the analysis.

APEXCARDIOGRAMS

The apexcardiogram was recorded from the point of maximum cardiac impulse with the patient in the left lateral position by a Cambridge transducer with a time constant of 4 seconds. The ratio of the height of the A wave to the total deflection (A/H) was calculated and the mean of three cardiac cycles recorded.

CARDIAC CATHETERISATION

The patients studied required coronary arteriography to assess their disease and the aortic valve had been crossed in all of them. The procedure was performed via either the brachial or femoral artery. Pressure was recorded before left ventricular angiography by a fluid filled 8F pigtail catheter attached to a manifold micromanometer transducer (Medex Medical). The left ventricular end diastolic

Table 1 Mean (SD) values of Doppler and M mode measurements in patients with left ventricular hypertrophy

	Controls	*Patients*
Age (yr)	50 (17)	58 (17)
RR intervals (ms)	930 (155)	850 (150)
A wave (m/s)	0·54 (0·12)	0·68 (0·29)*
E wave (m/s)	0·70 (0·18)	0·83 (0·29)
A/E ratio	0·79 (0·28)	0·91 (0·50)
Isovolumic relaxation time (ms)	60 (9)	65 (25)
Minimum dimension to mitral opening (ms)	36 (22)	72 (43)*
Percentage dimension change before mitral opening (ms)	5 (4)	17 (10)*
Peak dW/dt (cm/s)	10 (3)	6·4 (3)*
Peak dD/dt (cm/s)	16 (4·5)	9·3 (3·3)*
LV end diastolic dimension (cm)	5 (0·6)	4·8 (1·0)
Posterior wall thickness (cm)	0·86 (0·11)	1·2 (0·3)*
Septal thickness (cm)	1·0 (0·1)	1·6 (0·4)*
A/H ratio	0·18 (0·05)	0·27 (0·14)*
LV mass (g)	200 (50)	325 (145)*
Phase lag (ms)	68 (14)	66 (30)
Radius/thickness ratio	2·7 (0·4)	1·78 (0·6)*

*$p < 0{\cdot}01$.

pressure was taken as the point on the diastolic waveform at the onset of the QRS complex on the simultaneously recorded electrocardiogram. The mean of 10 cardiac cycles was recorded. All studies were done within 48 hours of the echocardiographic examination.

STATISTICAL ANALYSIS

Values are quoted as mean (SD). Relations between variables were analysed by least squares linear regression. Patients with left ventricular hypertrophy were, in addition, divided into three groups according to the A/E ratio (> 0·9, 0·6–0·9, < 0·6). The range 0·6–0·9 was used as an approximation of the 99% confidence limit of our normal range (0·63–0·94). Student's unpaired *t* test was used to compare group mean values.

Results

Tables 1 and 2 show mean values of the measurements.

M MODE MEASUREMENTS AND GENERAL DATA

Left ventricular mass (325 (145) *v* 200 (50) g) and wall thickness were, by definition, increased in patients with left ventricular hypertrophy. Relaxation was very incoordinate in hypertrophied hearts compared with normal, as shown by the long interval from minimum cavity dimension to mitral valve opening (70 (45) *v* 35 (20) ms) and a large increase in transverse dimension before the mitral valve was opened (17 (10) *v* 5 (4) %). The A/H ratio on the apexcardiogram was higher in the hypertrophy group (0·27 (0·14) *v* 0·18 (0·05). There were no significant differences in mean age, RR interval, isovolumic relaxation time, and phase lag between the patients and the controls.

Coronary arteriography was normal or showed minor irregularities only in 35 patients but in 12 the disease was severe enough to warrant coronary artery grafting. Patients with coronary artery disease were older (65 (8) *v* 56 (19) years) than those without and their isovolumic relaxation time was longer (80 (25) *v* 60 (20) ms, $p < 0{\cdot}05$). There were no other significant differences. Specifically, neither the interval from minimum cavity dimension to mitral valve opening (75 (40) *v* 70 (45) ms) nor the percentage change in transverse dimension before mitral valve opening (18 (12) *v* 16 (10) %) was different in the patients with coronary artery disease and those without.

SPECIFIC DIGITISED M MODE INDICES

Peak dD/dt (16 (4·5) *v* 9·3 (3·3) cm/s) and peak dW/dt (10·0 (3·0) *v* 6·4 (3·0) cm/s) were both significantly lower in patients with aortic stenosis than in the controls. They were consistently abnormal in hypertrophied hearts, even when the A/E ratio was apparently normal.

DOPPLER MEASUREMENTS

As a group, patients with left ventricular hypertrophy had a higher mean A wave velocity (0·68 (0·29) *v* 0·54 (0·12) m/s). However, the mean values for the A/E ratio and peak E wave velocity were not significantly

Table 2 Subgroup analysis of patients with left ventricular hypertrophy

	Left ventricular hypertrophy		
Variable	*Dominant E (A/E < 0·6) (n = 11)*	*Dominant A (A/E > 0·9) (n = 19)*	*Normal (0·6 < A/E < 0·9) (n = 17)*
Age (yr)	48 (19)*†	68 (8)	56 (18)
RR interval (ms)	810 (90)	880 (160)	830 (170)
A wave (m/s)	0·39 (0·24)*†	0·84 (0·22)	0·70 (0·24)
E wave (m/s)	1·0 (0·24)*†	0·62 (0·13)	0·95 (0·30)
A/E ratio	0·37 (0·22)*†	1·38 (0·39)	0·73 (0·09)
Isovolumic relaxation time (ms)	39 (23)*†	80 (15)	64 (22)
Minimum dimension to mitral opening (ms)	49 (21)*	96 (43)	51 (33)
Percentage dimension change before mitral opening (ms)	12 (10)*	21 (10)	15 (8)
Peak dW/dt (cm/s)	5·6 (2·9)	5·9 (2·4)	7·5 (4·0)
Peak dD/dt (cm/s)	10·3 (3·1)*	7·4 (2·7)	10·6 (3·4)
Left ventricular end diastolic dimension (cm)	5·3 (1·0)*	4·4 (0·8)	4·8 (1·1)
Posterior wall thickness (cm)	1·2 (0·4)*	1·1 (0·3)	1·3 (0·4)
Septal thickness (cm)	1·3 (0·4)*	1·8 (0·2)	1·5 (0·5)
A/H ratio	0·31 (0·16)	0·21 (0·1)	0·30 (0·14)
Left ventricular end diastolic pressure (mm Hg)	25 (10)	20 (9)	22 (6)
Peak aortic pressure difference (mm Hg)	70 (29)	60 (30)	66 (25)
Left ventricular mass (g)	320 (95)	320 (60)	330 (75)
Phase lag (ms)	58 (30)*	92 (30)	48 (34)

*$p < 0{\cdot}05$ *v* group with dominant A wave;
†$p < 0{\cdot}05$ *v* group with normal A/E ratio.

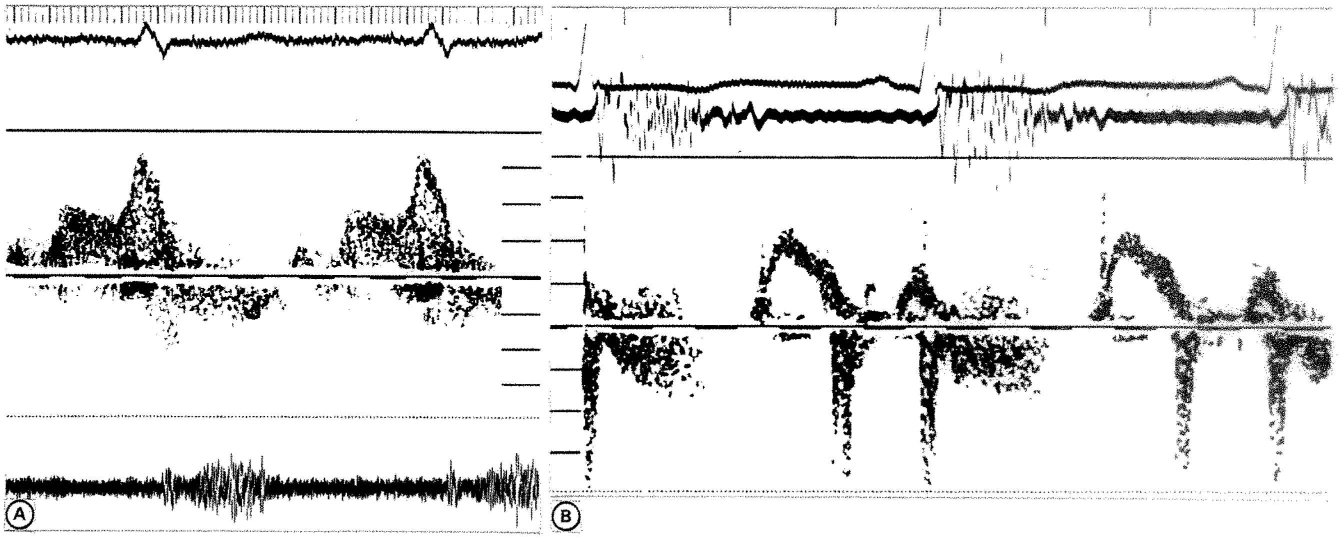

Figure 3 Pulsed Doppler recordings of transmitral flow velocity from two patients with left ventricular hypertrophy owing to aortic stenosis, showing the wide variation in A/E ratio in this condition. (A) A dominant A wave and (B) a dominant E wave. Full scale deflection is 4 kHz.

different in the controls and patients with left ventricular hypertrophy.

The Doppler A/E ratio varied widely in patients with left ventricular hypertrophy, ranging from a dominant E wave to a dominant A wave (fig 3). To investigate possible underlying factors, we divided the patients into three groups according to the A/E ratio, depending on whether it is greater, less than, or within the 99% confidence interval of normal. The group with a dominant E wave were younger (48 (19) *v* 68 (8) years), had a shorter isovolumic relaxation time (39 (23) *v* 80 (15) ms), a shorter interval from minimum cavity dimension to mitral valve opening (49 (21) *v* 96 (43) ms), a higher peak rate of dimension increase in early diastole (10·3 (3·1) *v* 7·4 (2·7) cm/s), a larger cavity size at end diastole (5·3 (1·0) *v* 4·4 (0·8) cm), a thinner septum (1·3 (0·4) *v* 1·8 (0·2) cm), and a smaller phase lag between dimension increase and transmitral flow (58 (30) *v* 92 (30) ms) than those with a dominant A wave (all p values < 0·05). The peak rates of posterior wall thinning and dimension increase were consistently abnormal across the three groups and there were no significant differences between them. The same applied to left ventricular end diastolic pressure, A/H ratio on the apexcardiogram, and the peak instantaneous aortic pressure difference.

Table 3 Regression analysis for patients with left ventricular hypertrophy

Variable	*A/E ratio*	*E wave velocity*	*Peak dD/dt*	*Peak dW/dt*
Dimensions				
Left ventricular end diastolic dimension	NS	NS	NS	NS
Radius to thickness ratio	NS	NS	NS	NS
Left ventricular mass	NS	NS	NS	
Isovolumic relaxation events				
Isovolumic relaxation time	p < 0·01 (30%)	p < 0·01 (27%)	NS	NS
Interval from minimum cavity dimension to mitral valve opening	p < 0·01 (50%)	NS	NS	NS
Percentage dimension change before mitral opening	p < 0·01 (22%)	NS	NS	NS
Age	p < 0·01 (16%)	NS	p < 0·01 (35%)	NS
Loading conditions				
Left ventricular end diastolic pressure	NS	NS	NS	NS
Peak left ventricle – aorta pressure difference	NS	NS	NS	NS

*Figures in brackets are the values for r^2.

REGRESSION ANALYSIS BETWEEN VARIABLES (TABLES 3 AND 4)

Age

The A/E ratio depended on age in both the controls and the patients with hypertrophied hearts; the regression equations for the two groups were indistinguishable. The A/E ratio thus varied with age in the same way in the normal and hypertrophied hearts.

In contrast, peak dD/dt was unrelated to age in the controls, but was sensitive to age in those with left ventricular hypertrophy. Peak dW/dt, though, was independent of age in both groups.

Isovolumic relaxation events

In patients with left ventricular hypertrophy the A/E ratio also correlated with events during isovolumic relaxation (isovolumic relaxation time, interval from minimum dimension to mitral opening, and percentage dimension change before mitral opening) and the E wave velocity correlated with the isovolumic relaxation time.

The peak rates of dimension increase (dD/dt) and wall thinning (dW/dt) by contrast were independent of events during isovolumic relaxation in both the normal and hypertrophied hearts.

Loading conditions

The Doppler A/E ratio, peak E wave velocity, and the digitised M mode indices (peak dD/dt, dW/dt) were independent of the left ventricular end diastolic pressure and the peak instantaneous aortic pressure difference.

Geometrical dimensions

Left ventricular end diastolic dimension, left ventricular mass, and radius to thickness ratio did not affect Doppler A/E ratio, E wave velocity, peak dD/dt, or peak dW/dt.

*Table 4 Significant regression equations**

y	*x*	*Slope*	*Intercepts*	r^2
		Controls		
A/E	Age	0·012 (0·0023)	0·18 (0·12)	54%
E	Age	−0·0073 (0·0016)	1·07 (0·090)	51%
		Left ventricular hypertrophy		
A/E	Age	0·012 (0·0042)	0·20 (0·25)	16%
A/E	Isovolumic relaxation time	0·0092 (0·0022)	0·28 (0·16)	30%
A/E	Interval from minimum dimension to mitral opening	0·0083 (0·0014)	0·37 (0·11)	50%
A/E	Percentage dimension change before mitral opening	0·022 (0·0076)	0·51 (0·15)	22%
E	Isovolumic relaxation time	−0·0057 (0·0015)	1·21 (0·10)	28%

*$p < 0·01$.

Discussion

For some years it has been realised that diastolic as well as systolic function may be abnormal in left ventricular disease and that it is possible to quantify such disturbances noninvasively. An early criterion was the diastolic closure rate of the normal mitral valve, as detected by M mode echocardiography.[8] While this was undoubtedly reduced in patients with various ventricular diseases, as a measurement it proved to be multifactorial and difficult to determine unambiguously, so its use in this way has been effectively abandoned. A second approach was to observe the rates of increase of cavity dimension and wall thinning by digitising M mode echocardiograms. This proved effective in delineating disturbed early diastolic function in several conditions, including left ventricular hypertrophy,[9] where the rate was reduced, and coronary artery disease, where wall motion appeared incoordinate.[10] These findings were validated by contrast angiography,[11] and confirmed by radionuclide[12] angiography. As cross sectional echocardiography has developed, however, and in particular as colour flow Doppler has appeared, M mode echocardiograms are recorded less and less frequently. The method is held to be time consuming and some find it difficult to obtain records of adequate quality for digitisation.[13]

During the same period, Doppler methods have been used more widely. They also allow early diastolic function to be inferred from the velocity of inflow into the ventricle, either in absolute terms, or, more commonly, as the ratio of velocity during atrial systole to that in early diastole (A/E ratio). In view of the M mode and other findings, it is not surprising that these Doppler measurements are also abnormal in patients with left ventricular hypertrophy. Peak early diastolic filling velocity was reduced and the A/E ratio increased. It seems that the two approaches measure the same disturbance, and so could be used interchangeably, with Doppler displacing M mode altogether. We designed the present study to examine whether this was so.

Despite their superficial similarity, our results show clear differences between methods based on M mode and Doppler when they are used to assess events during early diastole. Digitised M mode echocardiographic indices were consistently abnormal in patients with left ventricular hypertrophy, whereas those based on Doppler, either peak E wave velocity or A/E ratio, were not. In addition, the Doppler measurements, particularly A/E ratio, proved to be remarkably sensitive to events during isovolumic relaxation. When this was prolonged and incoordinate, due either to left ventricular hypertrophy or associated coronary artery disease, the peak E wave velocity fell and there was a shift in the proportion of the stroke volume entering the ventricle away from early diastole towards atrial systole. By contrast, the peak rates of dimension increase or wall thinning were unrelated to what had occurred during isovolumic relaxation. Finally, both groups of measurements were sensitive to age, but in a different way. A/E ratio increased to the same extent with age both in the controls and patients with aortic stenosis, whereas M mode based measurements in the controls were apparently insensitive to age. Age did, however, affect the M mode measurements in patients with aortic stenosis. It is clear, therefore, that the two types of measurement perform quite differently in this group of patients with left ventricular hypertrophy caused by a single, clearly defined entity (aortic stenosis), and therefore that they cannot be taken to be interchangeable.

If Doppler and M mode did indeed both measure early diastolic left ventricular filling rate, these differences would be hard to explain. However, both assess it only indirectly. Doppler echocardiography measures a peak velocity rather than a filling rate, and M mode measures a dimension rather than a volume. It is thus likely that in these indirect relations lies the explanation of our apparently conflicting results. Filling rate is related to blood velocity by cross sectional area; there is though no reason to suppose that this is consistently abnormal in patients with left ventricular hypertrophy unless the cavity shape is very distorted. It has previously been shown, however, that discrepancies between changes in cavity dimension and cavity volume are particularly obvious during early diastole. They are caused by a change in cavity shape with part, or even all the diastolic increase in cavity dimension occurring before mitral valve cusp separation and thus in the absence of volume change.[14] In these circumstances, the rapid early diastolic dimension increase and wall thinning measured by M mode echocardiography may still occur normally, and should thus be regarded as manifestations of an autonomous process normally coupled to filling. Rapid dimension increase and particularly rapid wall thinning may thus be a direct cause of rapid filling; they certainly do not depend on it. Even in healthy controls, the cavity dimension consistently leads flow velocity as measured by Doppler, again showing that it can potentially be separated from filling rate.[7] It was thus of interest that peak dimension increase and wall thinning rate proved so much more sensitive than Doppler in detecting disturbed rapid filling in patients with left ventricular hypertrophy.

The lack of sensitivity of the most commonly used Doppler measurement of ventricular diastolic function, the A/E ratio, seemed to have several causes. Though it was related to age, this relation was less strong than for the M mode measurements, and so could not have been the only cause of the very wide scatter seen in the patients with left ventricular hypertrophy. In patients with a dominant E wave, cavity size tended to be greater and wall thickness less, while isovolumic relaxation was shorter. This was not due to a high left ventricular end diastolic pressure. In approximately one third of patients the A wave was abnormally small or absent. This might suggest "left atrial failure", possibly because of chronically raised left atrial pressure. However, the relative height of the A wave on the apexcardiogram was normal or even increased in these patients, showing that left atrial mechanical activity was intact. The combination of a normal increase in atrial pressure as reflected in the apexcardiogram[15] with a lower than normal increase in volume thus strongly suggest that end diastolic left ventricular compliance was reduced in some patients with left ventricular hypertrophy. No such effect could be identified as influencing the M mode measurements.

At first sight, it is surprising that neither of the two sets of measurements were sensitive to loading conditions, as assessed by left ventricular end diastolic pressure. Not only is there much experimental evidence to suggest that such a relation should exist,[16 17] but, more importantly, it should follow directly from the physics of flow. Blood flow velocity, however, is not directly proportional to end diastolic pressure, but depends on Newton's Laws of motion. Blood velocity accelerates in response to a force, expressed in a liquid as a pressure gradient with the physical dimensions of mm Hg per cm. During early diastole, the pressure gradient is changing very rapidly as atrial and ventricular pressure approach one another. It is also affected by ventricular restoring forces, which effectively lower left ventricular pressure and are asymmetrically distributed throughout the ventricle. Rather than a simple pressure difference, therefore, pressures are likely to vary not only with time, but also in space, across the ventricular inflow. Finally, the pressure gradient relates to blood acceleration not blood velocity; velocity depends also on the time over which the acceleration has operated as well as on acceleration itself. It would thus be simplistic to suppose that these complex physical determinants of early diastolic flow could possibly be described by a single value of end diastolic pressure. It is thus not surprising that our results show no relation between the two. The absence of such a relation does not, of course, prove that blood flow is independent of loading conditions, but it does show that the appropriate loading conditions in humans are difficult to measure. If the early diastolic increase in transverse dimension and fall in wall thickness are autonomous processes, as suggested above, then one would not expect them to be related even to appropriate measures of loading conditions. Indeed, if they are related to restoring forces, they will contribute to the overall atrioventricular pressure gradient. For these quite different reasons, we were not surprised at finding no relation between left ventricular end diastolic pressure and either of our two sets of measurements.

Our results suggest that the relation between age and diastolic function in patients with left ventricular hypertrophy may be more complex than has previously been supposed.[18 19] In healthy controls M mode measurements did not depend on age; the relation seen in the patients with left ventricular hypertrophy, therefore, might be because in older individuals the hypertrophy has been more long standing and its functional disturbances more severe. This would imply that the natural course of left ventricular outflow tract obstruction is longer in the elderly, an assumption for which there is no evidence. Alternatively, the response to hypertrophy when the heart is young may differ from that when it is old. The Doppler results also give some support to this idea. Patients with lower A/E ratios were younger and though their ventricular mass was identical their cavity size was larger, and, in particular, late diastolic filling was often restricted. It is thus possible that the slowly filling ventricle with a prolonged isovolumic relaxation time and an accentuated A wave on Doppler is a feature not of hypertrophy alone, but of hypertrophy in the elderly. Younger patients seem to respond to hypertrophy with a more restrictive filling pattern. The peak early inflow velocity is maintained but that in late diastole falls, so the A/E ratio is low.

Our results thus show that M mode and Doppler measurements of early diastolic function are not identical in patients with left ventricular hypertrophy secondary to aortic stenosis. M mode measurements seemed more specific, in being unaffected by events during isovolumic relaxation and in discriminating more completely between normal and abnormal. They are less directly related to early diastolic transmitral flow rate, but may well reflect processes within the ventricular wall which underlie the restoring forces. Since ventricular filling is closely related to the effects of restoring forces, the two approaches to assessing early diastolic function can therefore be regarded as complementary rather than exclusive or interchangeable. Their combined use, especially with other non-invasive methods, is likely to be much more productive than that of either alone.

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Sensitivity and speed of colour Doppler flow mapping compared with continuous wave Doppler for the detection of ventricular septal defects

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Abstract

Twenty nine patients (aged from three months to 37 years) with confirmed or suspected ventricular septal defects were studied separately by three examiners who used colour flow mapping and imaging, or continuous wave Doppler and imaging, or a combined reference examination. Colour flow mapping identified 19 of the 25 patients with a ventricular septal defect, continuous wave Doppler echocardiography identified 18, and the combined reference examination identified 24. Two of four patients without ventricular septal defect had a false positive result with colour flow mapping and none had a false positive result with continuous wave Doppler examination. During the reference examination continuous wave Doppler identified 24 patients with ventricular septal defects and colour flow mapping identified 23. In two patients a second ventricular septal defect was found by colour flow mapping, and confirmed by continuous wave Doppler. There was no significant difference in time to diagnosis between the two techniques.

Colour flow mapping aids identification of multiple ventricular septal defects but is not faster and has lower specificity than continuous wave Doppler. A combination of the two techniques gave the highest sensitivity and specificity.

Colour Doppler flow mapping gives a graphical display of patterns of blood flow in two dimensions but it can be more difficult to interpret and more subject to error than continuous wave and single sample volume Doppler because of the large amounts of information displayed and the slower frame rate. Because it is a pulsed Doppler technique aliasing at high velocities causes ambiguity.

Colour flow mapping allows screening for abnormal flow of the entire two dimensional sector whereas continuous wave and pulsed Doppler examine only a given direction or point, respectively. For this reason, it has been suggested that colour flow mapping would be helpful in screening for lesions such as ventricular septal defects.

The current study was designed to compare the speed and accuracy of colour flow mapping and continuous wave Doppler for the diagnosis of ventricular septal defects when both are used in conjunction with cross sectional echocardiography.

Patients and methods

PATIENT SELECTION

We reviewed patient records or referrals for the diagnosis of suspected or actual ventricular septal defect and selected 29 outpatients, aged three months to 37 years (mean (SD) 6·2 (8·3) years). The distribution of diagnoses was 11 infracristal/perimembranous (one with moderate pulmonary stenosis), one supracristal, 10 muscular/trabecular (one associated with Ebstein's anomaly), two tetralogy of Fallot, one pulmonary atresia with ventricular septal defect, and four closed spontaneously or at operation. Patients with atrioventricular canal were excluded from the study. Only three patients had been catheterised.

EXAMINERS

We chose two test examiners who had more experience in the diagnosis of adult heart disease than with infants and children. The first test examiner was a technician with a total of 11 years' experience of echocardiography, ten years with Doppler echocardiography, and two with colour flow mapping, who used only cross sectional imaging and colour flow mapping to make a diagnosis. The second test examiner was a cardiology fellow with one year's experience of Doppler echocardiography, who used only cross sectional imaging and continuous wave Doppler to make a diagnosis. The third, or reference examiner, was a paediatric cardiologist with five years' experience in echocardiography/Doppler, who used the history, chart, physical examination, and cross sectional echocardiography, continuous wave Doppler, and colour flow mapping to reach the reference diagnosis. This examiner also used all ultrasound methods together and compared the optimal results with colour flow mapping and continuous wave Doppler.

EQUIPMENT

All examinations were performed with a mechanical, annular array, colour flow mapping system (CFM-700, Vingmed Sound, A/S).

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This system allows all the Doppler methods to be achieved with the same imaging transducer (3·5 MHz) and it also allows simultaneous imaging and continuous wave Doppler examination.

EXAMINATION PROTOCOL

Unsedated patients were examined independently by the test examiners. The examination was stopped when an experimental examiner and the reference examiner agreed that the diagnostic criteria were met, or after 15 minutes. The time and diagnosis were recorded for each examination. If there was no conclusion, an examination time of 15 minutes was recorded. Unlike the reference examiner, the experimental examiners did not have access to any information about the patient or the results of other examinations, other than that the patient had a suspected ventricular septal defect.

After both of the experimental examiners completed their examinations, the reference examiner used all available data, and supplementary echocardiographic or Doppler examinations when necessary, to determine the final diagnosis. During this final examination, he attempted to show the lesion by both methods, if necessary using the other as a guide to determine the absolute sensitivity.

The diagnostic criteria for a ventricular septal defect were as follows: *for flow mapping*—the presence of flow that clearly passed through the ventricular septum, systolic disturbed flow ("mosaic pattern") on the right side of the septum, or a clear defect on the imaging examination were each considered sufficient; *for the continuous wave Doppler examination*—systolic flow directed towards the transducer with a velocity > 3 m/s, or a clear defect on cross sectional echocardiography were each considered sufficient. These criteria for continuous wave Doppler examination would miss patients with high right sided pressures and a ventricular septal defect too small to be seen on cross sectional imaging; however, none of the patients in the study population had this combination of features.

The classification of the patients was based on a total evaluation by the reference examiner. But the results of the reference examination were based on a strict interpretation of the reference examiner's results using the criteria of the study, which meant that both false positive and negative results were possible.

There were no disagreements over the diagnoses. In two patients the time to diagnosis was extended for the flow mapping examination because a test examiner and the reference examiner did not agree that the diagnostic criteria had been met. The examiners generally used the parasternal and subcostal approach but individual examiners were free to use whatever view they wished.

Number of positive and negative diagnostic examinations for each combination of actual diagnosis (left column) and type of examination

					Reference examiner			
	Colour flow mapping		*Continuous wave*		*Colour flow mapping*		*Continuous wave*	
Diagnosis	*Pos*	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*
VSD	19	6	18	7	23	2	24	1
No VSD	2	2	0	4	0	4	0	4

VSD, ventricular septal defect

STATISTICAL ANALYSIS

The times that it took to reach a diagnosis for each patient with continuous wave Doppler and colour flow mapping were compared by Student's paired *t* test.

Results

The table shows the diagnostic results. In 25 patients a ventricular septal defect was the final diagnosis. Of these, 19 were diagnosed by colour flow mapping and 18 by continuous wave Doppler. Of the patients with a false negative diagnosis on both examinations, one had pulmonary atresia and low velocity through a moderate sized defect, one had a supracristal defect, and four had muscular defects. The one patient in whom a ventricular septal defect was detected by flow mapping but not by continuous wave had a muscular defect.

All four patients without ventricular septal defects were correctly classified by continuous wave Doppler examination, but in two colour flow mapping incorrectly identified ventricular septal defects. Both of the false positive diagnoses arose because disturbed flow on the right side of the septum simulated a small muscular ventricular septal defect.

All except one patient with a ventricular septal defect were identified when the reference examiner used continuous wave Doppler echocardiography. The false negative result arose in a patient with a supracristal defect with flow directed towards the pulmonary valve that did not meet any of the diagnostic criteria. Twenty three defects were identified by colour flow mapping. The additional false negative was a small muscular defect. The small number of false positives and false negatives in the test and reference examinations precluded statistical testing for differences.

The time to diagnosis was 4·8 (5·9) minutes for the colour flow mapping examination and 5·8 (5·9) minutes for the continuous wave Doppler examination. This difference was not statistically significant. The mean difference in time to diagnosis between the two techniques was 0·9 (3·4) minutes, and it was not significantly different from zero ($p > 0{\cdot}2$). In only three patients was a conclusion reached after more than five minutes (maximum 11 minutes) of flow mapping, and similarly, only three patients needed more than five minutes of examination by continuous wave Doppler echocardiography (maximum eight minutes).

We found a second, unsuspected septal defect by colour flow mapping in two of the patients with a ventricular septal defect; both were confirmed by continuous wave Doppler examination. In one the second defect was from the left ventricle to right atrium and seemed to be more important than the original defect; the other was a small muscular defect.

Discussion

The addition of pulsed Doppler to cross sectional imaging has improved the diagnostic sensitivity of echocardiography for ventricular septal defects.[1-3] Continuous wave Doppler has also been used to diagnose ventricular septal defects, and it also gives information about physiological variables.[4-7]

Colour Doppler flow mapping has been used to identify ventricular septal defects,[8 9] and it seems to be especially good at identifying multiple ventricular septal defects.[10] It can clearly show the pattern of flow both through the septum and into the other heart chamber. The relative sensitivity of the various techniques is unknown, however. In the hands of experienced examiners both pulsed Doppler and colour flow mapping were highly sensitive and specific for the detection of ventricular septal defects in patients selected for catheterisation.[10] This population tended to have larger defects, and it seems reasonable to assume that errors would be more likely with the smaller lesions that are seen in a less selected patient group.

We found that the identification of ventricular septal defects by an experienced examiner with continuous wave Doppler was easy in almost all patients, whereas pulsed Doppler tends to be more difficult, leading to more potential false negatives.[11] One reason for this is that all depths in the direction of the beam are examined simultaneously by continuous wave Doppler; with pulsed Doppler the sample volume must be moved to each depth. Any improvement in speed and accuracy with colour flow mapping over the continuous wave examination is more likely in observers who were less experienced in congenital heart disease and who would be less certain of the continuous wave examination. We found that the continuous wave Doppler examination performed by such an examiner was as sensitive, fast, and may have been less liable to give false positive results than the flow mapping examination. On the other hand, the colour flow mapping examination identified previously unknown multiple ventricular septal defects. The best approach to achieve the highest sensitivity and specificity would be to use the two techniques to supplement one another.

The reference examiner had one false negative continuous wave Doppler examination. This was in a patient with a supracristal ventricular septal defect that caused turbulent, high velocity flow through the pulmonary valve and simulated pulmonary stenosis; it did not meet any of the diagnostic criteria of the study. Another false negative on cross sectional Doppler examination was caused by a small apical defect. The cause of the false positives on cross sectional Doppler examination is unclear, but one potential cause was flow disturbance around right ventricular septal trabeculae.

The greater sensitivity of the continuous wave Doppler examination in experienced hands for finding ventricular septal defects may be because it has a better time resolution than colour flow mapping.

For this study we used a single model of ultrasound machine and transducer with only one colour flow map. Because the use of different colour flow maps will change the operator's perception of normal and disturbed flow it can influence sensitivity. Clearly, the characteristics of the transducer and instrument also affect the absolute sensitivity of the techniques as well as their relative sensitivity. This means that our results cannot be extrapolated to all combinations of instrument and transducer, though in our opinion the intrinsic characteristics of colour Doppler flow mapping and continuous wave Doppler account for their relative strengths and weaknesses.

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Role of intraoperative ultrasound examination in patients undergoing a Fontan-type procedure

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Abstract

To determine its potential impact on perioperative surgical management intraoperative ultrasound examination (cross sectional imaging, colour flow mapping, pulsed and continuous wave Doppler) was used in 16 consecutive patients undergoing a Fontan-type procedure. Epicardial cross sectional imaging before bypass defined the precise intracardiac morphology in 15 of 16 patients. The preoperative morphological diagnosis was refined in four patients (25%), and this influenced surgical management in two (12%). Epicardial studies after bypass identified seven residual haemodynamic lesions in five patients (three residual intercardiac shunts, one ventricular outflow obstruction, one pulmonary artery obstruction, two mitral valve regurgitation), and led to immediate revision during a second period of bypass in three (18%). In one patient who required early reoperation residual shunting was not detected after bypass by either colour flow mapping or a contrast study. Final intraoperative studies showed a good surgical result in 14 patients (87%). Flow characteristics and flow velocities within the Fontan circulation could be assessed immediately after the patient came off cardiopulmonary bypass by means of combined pulsed wave Doppler and colour flow mapping in 14 of the 16 patients. Cross sectional studies of the left heart after bypass showed no change in ventricular function and allowed monitoring of volume replacement and ventricular filling.

Intraoperative ultrasound was a valuable monitoring technique in patients undergoing a Fontan-type procedure. It refined preoperative diagnosis, monitored ventricular function, and identified or excluded residual haemodynamic lesions in most patients.

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The Fontan procedure or one of its modifications is widely used to correct a wide range of complex congenital heart lesions.[1–3] Both the operative mortality and reported results in the intermediate term have improved remarkably over the past decade.[3–5] In several large series of patients,[4–6] however, residual haemodynamic lesions were common (14–29%) and some caused early deaths in hospital, required early reoperation, or impaired functional capacity.[7–9] We need an intraoperative monitoring technique for the rapid and accurate identification of important residual lesions immediately after a Fontan circulation has been established. This would allow the repair of important residual lesions during the same operation in a second period of bypass, and might further improve the early results of operation.

During operations for congenital heart disease high resolution epicardial cross sectional imaging can be used to define abnormal cardiac morphology before bypass and a combination of colour flow mapping and spectral Doppler investigations can be used to assess the haemodynamic results achieved by the surgical repair.[10–12] Epicardial cardiac ultrasound might also be useful for the immediate evaluation of the results achieved by a Fontan-type procedure. To test this premise we used the full range of ultrasound investigations in a series of patients undergoing a Fontan-type procedure.

Patients and methods

Sixteen patients who underwent a Fontan-type procedure at the Department for Cardiothoracic Surgery, Erasmus University, Rotterdam were entered into a prospective intraoperative ultrasound study to determine the impact of such an examination on perioperative surgical management.

PATIENTS

The age at operation ranged from 5 months to 33 years (median age 3 years 6 months) and the body weight ranged from 4400 g to 73 kg. The preoperative diagnosis (table 1) was absent right connection (tricuspid atresia) in 10 patients, double inlet left ventricle in four patients, "criss-cross" heart in one patient (case 3), and a congenitally corrected transposition (discordant-discordant connections) with a straddling tricuspid valve in one patient (case 13). All patients had situs solitus of the atria; four patients had dextrocardia. Two patients (cases 10 and 16) were known to have mild mitral valve regurgitation before operation.

Eleven patients had had palliative procedures (nine left Blalock shunts, one right Blalock shunt, two central shunts, one Waterston shunt, one pulmonary artery banding, one enlargement of a ventricular septal defect (table 1).

Table 1 Patient data, diagnosis, previous palliation, and surgical procedure

				Surgical procedure	
No	*Age*	*Preoperative diagnosis*	*Previous palliation*	*Fontan*	*Associated*
1	4 yr 5 mnth	DILV, VA disc, dextrocardia, outlet VSD	Nil	I	Direct TV closure
2	2 yr 5 mnth	TA, VA conc, ASD II	Left Blalock	I	Direct ASD closure
3	4 yr 5 mnth	AV conc, VA disc, ("criss-cross") multiple muscular VSDs, ASD II	Nil	I	Direct TV closure, Direct ASD closure
4	3 yr 11 mnth	TA, VA disc, dextrocardia, ASD II, restrictive VSD	Nil	I	Direct ASD closure, enlargement VSD
5	33 yr	DILV, VA disc, outlet VSD	Nil	I	Direct TV closure
6	3 yr 3 mnth	DILV, VA disc, dextrocardia, VSD, ASD II	Left Blalock	II	—
7	2 yr 9 mnth	TA, VA conc outlet VSD, ASD II	Left Blalock	III	Direct ASD closure
8	2 yr 9 mnth	TA, VA conc, ASD II	Left Blalock	IV	Direct ASD closure
9	3 yr 4 mnth	TA, VA disc, dextrocardia, ASD II, VSD, peripheral pulmonary stenosis	Left Blalock	I	Direct ASD closure, patch enlargement PA
10	15 mnth	DILV, VA disc, ASD II, restrictive VSD, mild MR	Banding	I	Single patch TV and ASD, enlargement VSD
11	4 yr 10 mnth	TA, VA conc, ASD II	Right and left Blalock	V	Direct ASD closure
12	5 mnth	TA, VA conc, ASD II, muscular VSD	Nil	V	Direct ASD closure, patch closure VSD
13	3 yr 10 mnth	AV disc, VA disc, straddling TV, ASD II, perimembraneous inlet VSD	Left Blalock	II	—
14	1 yr 9 mnth	TA, VA conc, ASD II, pulmonary atresia	Waterston	II	—
15	5 yr 9 mnth	TA, VA conc, ASD II, VSD	Left Blalock, central shunt	I	Direct ASD closure
16	11 yr 3 mnth	TA, VA conc, ASD II, muscular VSDs, mild MR	Left Blalock, central shunt, VSD enlargement	V	Patch/direct closure VSD, direct closure ASD

ASD II, secundum atrial septal defect, AV, atrioventricular; conc, concordance, disc, discordance; DILV, double inlet left ventricle, MR, mitral regurgitation, PA, pulmonary artery; TA, tricuspid atresia; TV, tricuspid valve, VA, ventriculoarterial; VSD, ventricular septal defect, Fontan procedures. I = direct atriopulmonary anastomosis; II = total cavopulmonary connection; III = modified Kreutzer procedure; IV = valved (homograft) atriopulmonary connection, V = valved (homograft) atrioventricular connection.

OPERATION

The surgical techniques used to achieve systemic venous to pulmonary artery connections (Fontan-type procedures) were (*a*) direct atriopulmonary anastomosis (retroaortic) in eight patients, (*b*) total cavopulmonary connection[13] by use of a prosthetic patch (three patients), (*c*) a Kreutzer procedure (right atrial appendage to main pulmonary artery connection incorporating the pulmonary valve) in one patient, (*d*) valved atriopulmonary connection (homograft conduit) in one patient with tricuspid atresia and a hypoplastic main pulmonary artery, and (*e*) valved atrioventricular connection (homograft conduit) in three patients with tricuspid atresia and ventriculoarterial concordance (table 1).

Secundum type atrial septal defects in 10 patients with tricuspid atresia were closed by means of a double layer of running sutures in nine patients. The defect was left open in one patient who underwent an operation for total cavopulmonary connection (case 2). Eight patients with tricuspid atresia had concordant ventriculoarterial connections. Three of these underwent an operation to construct a valved atrioventricular connection; this required closure of ventricular septal defect(s) in two (cases 12 and 16). Enlargement of a restrictive ventricular septal defect was required in one (case 4) of two patients with ventriculoarterial discordance.

All four patients with double inlet left ventricle had ventriculoarterial discordance. Three of these underwent a direct atriopulmonary anastomosis. The tricuspid valve was closed with a double layer of interrupted mattress sutures in two patients with an intact atrial septum (cases 1 and 5) and a pericardial patch was used to close both the tricuspid valve and the secundum atrial septal defect in one (case 10). This latter patient also required enlargement of a restrictive ventricular septal defect because of ventriculoarterial discordance. One patient with double inlet left ventricle (case 6) underwent an operation to form a total cavopulmonary connection; the atrial septal defect was left open.

One patient with a preoperative diagnosis of "criss-cross" heart (case 3) underwent direct atriopulmonary anastomosis with direct closure of both the tricuspid valve and the atrial septal defect. The patient with congenitally corrected transposition and a straddling tricuspid valve (case 13) underwent a total cavopulmonary anastomosis, without closure of the atrial septal defect.

ECHOCARDIOGRAPHY

Intraoperative epicardial studies were performed with a Toshiba SSH 65 or a Toshiba SSH 160 A ultrasound system in all 16 patients before and after cardiopulmonary bypass. The scanning equipment consisted of multiple standard precordial transducers: a 5 MHz transducer for high resolution cross sectional imaging plus a 3·75 MHz transducer for colour flow mapping and pulsed wave Doppler investigations, and in two patients a 2·5 MHz continuous wave Doppler duplex probe. The probes and wires were packed in sterile tube-shaped plastic bags after about 5 ml of sterile ultrasound coupling gel had been applied to the tip of the transducer. After packing, the probes were passed into the operative field where they remained during the entire operation.

Studies were performed either by a paediatric cardiologist or the cardiac surgeon and were entirely recorded on video tape to allow subsequent off line interpretaton. The studies before bypass lasted about 5 minutes and those after bypass about 10 minutes. The studies were interpreted on line and the findings were discussed. Immediately after completion further off line analysis was carried out in the echocardiography laboratory.

Pre-bypass studies were performed after median sternotomy and pericardiotomy. Warm saline was poured into the pericardial cradle to improve contact between the epicardium and the transducer and to reduce mechanical irritation of the heart. Cross sectional imaging was performed first. Results were correlated with the preoperative findings and with the findings at surgical inspection. Then haemodynamic function was assessed by colour flow mapping of the entire heart. These morphological and haemodynamic ultrasound findings served as a reference for the subsequent studies after bypass.

Post-bypass studies were performed after the removal of all cannulas for cardiopulmonary bypass, because these may cause unpredictable flow patterns, and as soon as haemodynamic function was relatively stable. Cross sectional imaging was used to assess the surgical repair and together with M mode tracings to monitor ventricular function. Colour flow mapping of the entire heart and the Fontan circulation was used to detect any flow obstructions across the anastomoses, residual intracardiac shunting, incompetence of atrioventricular valves, or ventricular outflow obstructions. Pulsed wave Doppler investigations were performed to trace and measure flow velocities across the Fontan circulation. Continuous wave Doppler was used to assess blood flow through the ventricular septal defect in two patients with ventriculoarterial discordance. Contrast echocardiographic studies, for the exclusion of residual interatrial shunting, were performed to confirm the findings at colour flow mapping. Routinely 2–5 ml of hand-agitated patient's blood was used as the contrast medium. This was injected via a right atrial line while a modified four chamber view was scanned from the mid-portion of the right ventricle.

Results

STUDIES BEFORE BYPASS

A combination of high resolution cross sectional epicardial imaging and colour flow mapping confirmed the preoperative diagnosis in 11 of the 16 patients. The diagnosis was refined in four patients (25%), and this influenced surgical management in two (12%) (table 2). In one of these patients (case 3) both atrioventricular valves and their tensor apparatus were shown to be entirely connected to the left ventricle, changing the preoperative diagnosis of "criss-cross" heart to double inlet left ventricle. This new finding was, however, of no surgical relevance. In one patient (case 7) with a secundum type atrial septal defect an additional low posterior fenestrated defect was detected. In two patients (cases 11 and 16) with ventriculoarterial concordance epicardial cross sectional imaging clearly showed a right ventricular chamber of moderate size and good function plus the absence of any valvar or subvalvar obstruction. This information, in both patients scheduled for construction of a direct atriopulmonary connection, allowed the outlet chamber to be incorporated into the Fontan circulation.

The information obtained by cross sectional imaging before bypass was verified at surgical inspection whenever feasible, and was found to be exact and complete in 15 out of 16 patients. In one patient with multiple muscular ventricular septal defects (case 16) the epicardial study before bypass showed only one large muscular defect and did not identify the additional defects. These were only identified at surgical inspection after the muscular obstruction between the trabecular and outlet portions of the right ventricle had been relieved. Colour flow mapping before bypass allowed assessment of haemodynamic function immediately before the repair and, even more importantly, served as the reference for interpretation of the subsequent study after bypass.

STUDIES AFTER BYPASS

Table 3 lists the residual lesions identified and their surgical consequences.

Atrial septal defects

After repair the perfect closure of atrial septal defects was assessed by colour flow mapping along a series of foreshortened four chamber views from the right ventricular and right atrial epicardium. A residual defect at the postero-inferior border of the surgical closure site (direct suture) was detected in one patient (case 7; table 2) in whom an additional low posterior fenestrated defect was found before bypass. Colour flow mapping showed its precise site and the restrictive flow pattern of the continuous right-to-left shunt. Residual shunting was reconfirmed by contrast injection into the right atrial line. Immediate revision during a second period of bypass effected closure of the defect; this was confirmed by colour flow mapping and a contrast study (fig 1).

Ventriculoatrial communications

Colour flow mapping studies after bypass showed a residual ventriculoatrial communication in one patient (case 5). A high velocity jet

Table 2 Refinement of the preoperative diagnosis by studies before bypass and influence on surgical management

No	*Preoperative*	*Study diagnosis before bypass*	*Influence on surgical management*
3	Criss cross heart	Double inlet left ventricle	No influence
7	Secundum ASD	Additional low posterior fenestrated ASD	No influence
11	Size and morphology of RV chamber unknown, intact IVS	RV of good size, no infundibular stenosis, normal PV	Valved atrioventricular connection
16	Size and morphology of RV chamber unknown	RV chamber of good size	Valved atrioventricular connection

ASD, atrial septal defect; IVS, interventricular septum; PV, pulmonary valve; RV, right ventricle.

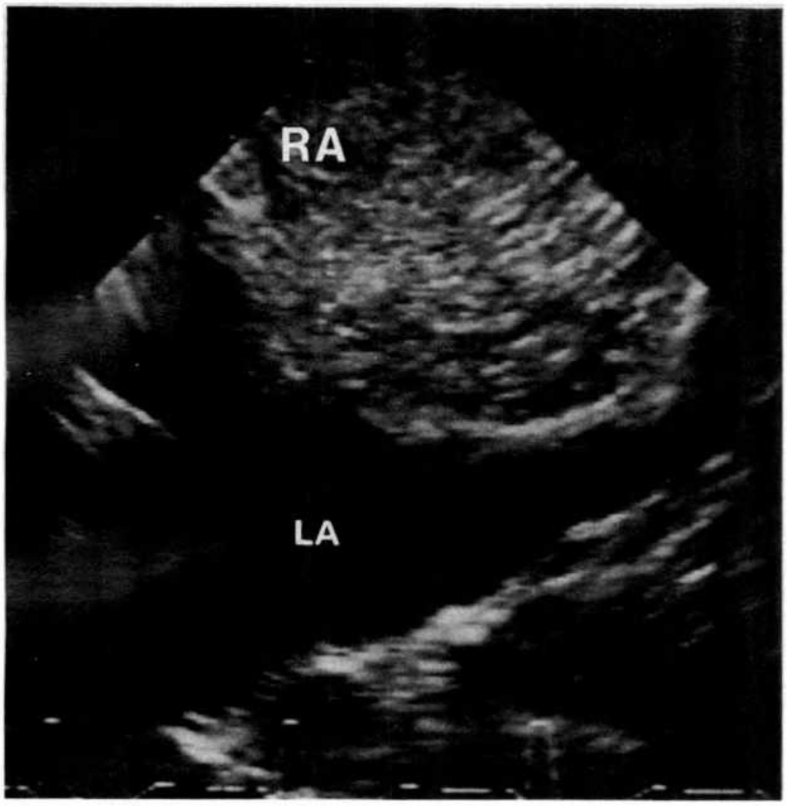

Figure 1 Contrast echocardiographic study after immediate revision of a small residual interatrial shunt (patient 7). After right atrial injection of hand agitated contrast medium, the right atrial cavity was uniformly opacified, whereas there was no sign of contrast in the left atrium. This showed the perfect closure of the residual defect. LA, left atrium; RA, right atrium.

originating from the site of primary closure of the right atrioventricular valve was shown to reach far into the cavity of the right atrium. Immediate revision during a second period of bypass (pericardial patch closure) achieved perfect closure of the tricuspid valve. In the remaining three patients who underwent closure of a right sided atrioventricular valve colour flow mapping excluded any residual communication; this was reconfirmed by contrast studies (left atrial injection) in two.

Leakage from intra-atrial tunnels

In three patients a total cavopulmonary connection was created. Cross-sectional imaging after bypass showed the course of the tunnel, both venae cavae, and the anastomoses with the pulmonary artery system in two of the three patients. The colour flow mapping studies that were used to exclude residual shunting were judged to be satisfactory in only one patient. Studies after bypass were limited by the altered geometry of the right atrium and the flow masking properties of the prosthetic material used in the repair. Contrast studies with injection into the right atrial line gave one false negative and one false positive result. Postoperative studies in the intensive care unit (contrast and oxygen saturations) showed residual shunting in one patient (false negative result after bypass), who subsequently underwent reoperation. At reoperation residual communications through the small trabeculations were found between the base of the right atrial appendage and the linea terminalis. The suture line of the patch was found to be intact.

Ventricular septal defects

In seven of the eight patients with ventriculoarterial discordance, colour flow mapping and pulsed and continuous wave Doppler studies after bypass showed an unobstructed ventricular outflow. In one patient the ventricular septal defect was found to be severely restrictive after bypass, whereas it had been shown to be unrestrictive both before operation and during studies before bypass. The maximal flow velocity measured by continuous wave Doppler was about 3·8 m/s, representing a pressure gradient of about 58 mm Hg. Immediate revision during a second period of bypass reduced the pressure gradient to 12 mm Hg.

Two of three patients with tricuspid atresia and ventriculoarterial concordance who had valved atrioventricular connections created had patch closure of a ventricular septal defect. In one of these patients (case 16) additional muscular defects were found at surgical inspection and subsequently closed. The cross sectional imaging study after bypass showed a small residual muscular defect. Off line analysis of the study after bypass showed systolic left-to-right shunting and diastolic right-to-left shunting (fig 2) caused by raised right atrial and ventricular pressures.

Fontan circulation

Cross sectional imaging did not show any anatomical obstruction to the pulmonary artery flow in 14 of 15 patients with satisfactory studies. In one patient (case 14) the study was incomplete after total cavopulmonary connection. Evidence of homograft valve closure was found in all three patients with an atrioventricular connection (cases 11, 12, and 16) and pulmonary valve closure in the patient with a Kreutzer procedure (case 7). The valve leaflets

Table 3 Identification of residual lesions by colour flow mapping and Doppler studies after bypass and the surgical consequences

No	*Diagnosis*	*Surgical procedure*	*Residual lesion*	*Immediate revision*
5	DILV, AV disc, unrestrictive VSD	Atriopulmonary conn, direct closure of TV	Ventriculoatrial shunt, restrictive VSD	Patch closure TV, VSD enlargement
7	TA, VA conc, VSD, ASD II, additional fenestrated ASD	Modified Kreutzer, direct suture ASDs	Residual interatrial shunt at posteroinferior border	Re-closure
10	DILV, VA disc, ASD II, restrictive VSD, mild MR	Atriopulmonary conn, single patch TV, ASD, enlargement VSD	MR (increased)	No
15	TA, VA conc, ASD II, VSD	Atriopulmonary conn, direct suture ASD	Compression of left pulmonary artery	Patch enlargement of bifurcation
16	TA, VA conc, ASD II, muscular VSDs, mild MR	Atrioventricular conn, direct closure ASD, patch closure large VSD, direct suture apical VSD	Residual muscular VSD, MR (unchanged)	No

DILV, double inlet ventricle of left ventricular morphology; TA, tricuspid atresia; ASD II, secundum type atrial septal defect; VA, ventriculoarterial; conc, concordance; disc, discordance; VSD, ventricular septal defect; TV, tricuspid valve; conn, connection; MR, mitral regurgitation.

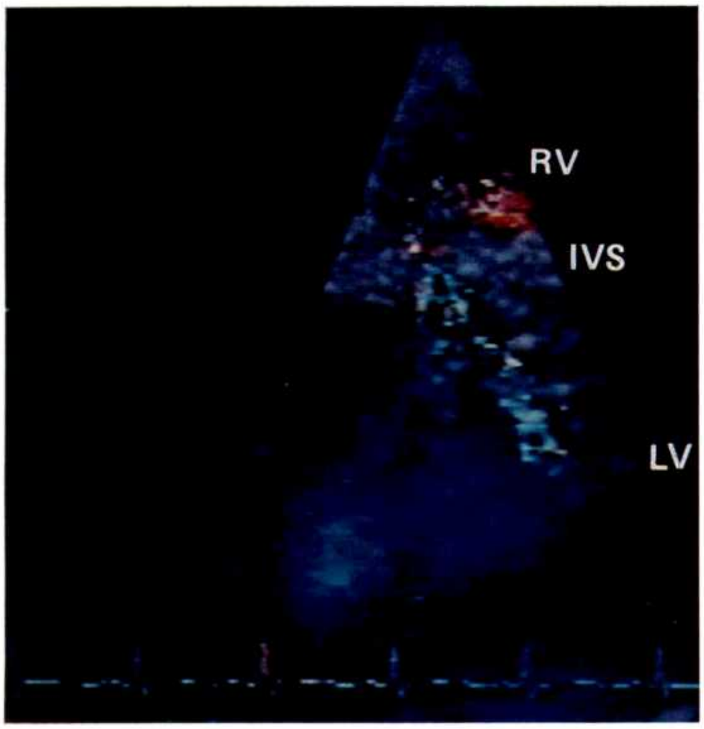

Figure 2 Residual interventricular shunting detected by colour flow mapping in patient 16 with tricuspid atresia, ventriculoarterial concordance, and multiple muscular ventricular septal defects. The mid-diastolic frame shows right-to-left shunting on the ventricular level (encoded in blue) with some flow turbulence. RV, right ventricle; IVS, interventricular septum; LV, left ventricle.

remained partly open in the one patient (case 8) in whom a valved atriopulmonary connection had been constructed.

Colour flow mapping showed laminar (that is, unobstructed) flow within the Fontan circulation in 13 of 14 patients with satisfactory studies. Studies were unsatisfactory in two patients with total cavopulmonary connections (cases 13 and 14). In one patient (case 15), in whom cross sectional imaging showed a narrow left pulmonary artery, colour flow mapping showed considerable obstruction at the origin of the left pulmonary artery (fig 3A). Pulsed wave Doppler echocardiography showed continuous turbulent flow distal to the obstruction with a velocity of 1·5 m/s, representing a pressure gradient of about 4–5 mm Hg. The stenosis was caused by compression from the ascending aorta. This was proved when anterior displacement of the aorta resulted in laminar unobstructed flow (fig 3B). Subsequent patch enlargement of the bifurcation during a second period of bypass established unobstructed laminar flow into the left pulmonary artery (fig 3C), with a maximal flow velocity of less than 1·0 m/s (fig 3D).

We assessed blood flow velocities and flow patterns within the Fontan circulation after bypass by pulsed wave Doppler investigations. Sample volumes were placed distal to the anastomoses or distal to any valve incorporated in the circulation. In patients with direct atriopulmonary anastomoses blood flow was found to be biphasic and bidirectional. Peak flow velocities ranged from 0·4 to 0·65 m/s and occurred during late diastole. The second peak occurred during late ventricular systole and ranged from 0·2 to 0·3 m/s. Retrograde flow was detected during early ventricular systole and early diastole. After total cavopulmonary anastomosis a non-pulsatile, low velocity flow pattern with considerable respiratory changes was noted. Two patients with valved atrioventricular connections (cases 11 and 12) showed biphasic forward flow, with velocity peaks in the main pulmonary artery of 0·25 and 0·3 m/s during late diastole and of 0·6 and 0·9 m/s during ventricular systole, indicating the contribution of the right ventricle to pulmonary blood flow. In the third patient with a valved atrioventricular connection (case 16) no ventricular augmentation was noted.

Mitral valve regurgitation

Mild mitral valve regurgitation was shown by colour flow mapping in two patients immediately after bypass. One patient (case 10) showed atrioventricular dissociation, necessitating epicardial pacing. The regurgitant jet was considerably larger than that shown during the study before bypass. In the second patient (case 16) the severity of mitral regurgitation was judged to be unchanged.

Ventricular function

Left ventricular function was assessed before and after bypass by a series of short axis scans through the left ventricle. No regional wall motion abnormalities were noted in any patient and ventricular function was unchanged compared with the studies before bypass. In four patients short axis scans were used to monitor volume replacement and ventricular filling while the patient was weaned from cardiopulmonary bypass. In a further two patients the studies helped to determine the dosage of inotropic support.

Complications

Complications induced by direct contact epicardial imaging, apart from occasional episodes of self terminating short runs of ventricular extrasystoles (maximum five in succession), were not encountered. Medical treatment or electical cardioversion were never required. Sterility was preserved by packing the probes into long sterile plastic bags. No episode of endocarditis, pericarditis, or mediastinitis was reported during the study period.

Discussion

We studied the impact of intraoperative echocardiography in patients undergoing a Fontan-type procedure on perioperative surgical management.

Cross sectional imaging before bypass allowed detailed insights into the individual intracardiac morphology and contributed to surgical management in 12% of the patients. In one case the diagnosis before bypass was incomplete because additional muscular ventricular septal defects were not shown; turbulent flow in the entire small right ventricular cavity prevented the recognition of multiple individual jets by colour flow mapping.

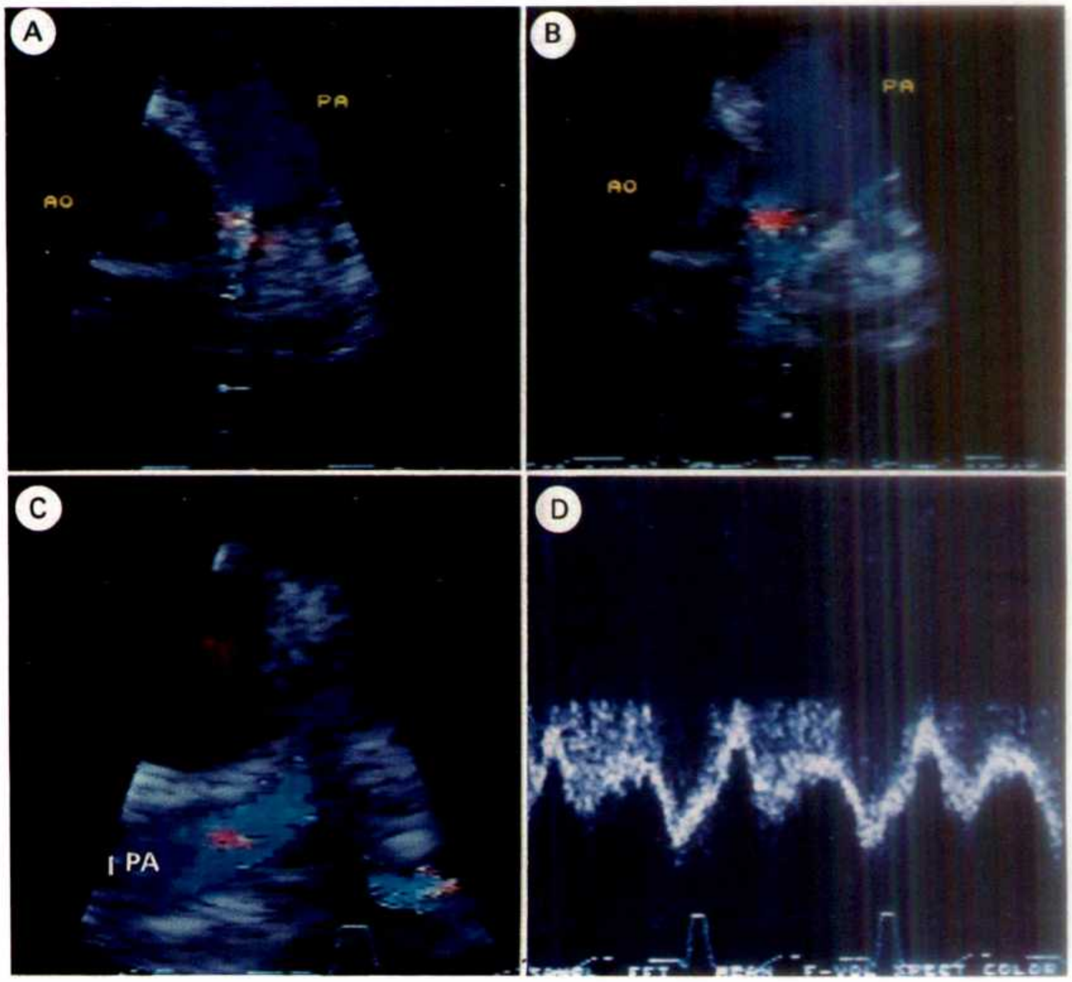

Figure 3 Study after bypass in patient 15 with severe pulmonary artery obstruction. (A) Colour flow mapping showing continuous turbulent flow just distal to the bifurcation caused by compression by the ascending aorta. (B) Lifting up of the aorta allows laminar, unobstructed flow in the left pulmonary artery, establishing the cause of obstruction. (C) After patch enlargement of the bifurcation and the proximal left pulmonary artery flow was unobstructed. (D) Pulsed wave Doppler sampling showed unobstructed flow. The maximal flow velocity was less than 1 m/s. Ao, ascending aorta; l, left; PA, pulmonary artery.

Ultrasound studies after bypass proved to be a valuable technique for the assessment of the surgical repair performed, for monitoring left ventricular filling and function, and for the exclusion of residual haemodynamic lesions. The modern range of Doppler ultrasound techniques, in particular colour flow mapping, are sensitive methods for the detection of abnormal intracardiac flow patterns. The use of these techniques immediately after bypass can detect even slight flow abnormalities.[14] In most patients undergoing total correction of congenital heart disease these minimal flow disturbances are not of surgical importance, whereas when the Fontan operation or one of its modifications is performed in patients with complex intracardiac anatomy or in younger patients, even small residual lesions can be clinically important. The immediate detection of these lesions and the subsequent repair during the same operation can improve the early surgical results.

Colour flow mapping allows the detection or definite exclusion of residual intracardiac shunting in most patients. The technique not only shows the existence of residual shunting but also defines the site of origin, which is impossible by any other technique. But the presence of prosthetic material used in the repair causes flow masking. After the creation of a total cavopulmonary connection both the change of the geometry of the right atrium and the use of prosthetic material precluded reliable colour flow mapping studies performed to exclude residual shunting in two of three patients. Thus after bypass the exclusion of leakage from the intra-atrial tunnel relied entirely on contrast studies. In retrospect we believe that one false positive contrast finding was related to the position of the right atrial line outside the tunnel; because there was an atrial septal defect the line was in what was functionally a pulmonary venous atrium. Sampling for oxygen saturations showed no desaturation and no further steps were taken. The second patient had only one contrast injection into a right atrial line, after which only a few microbubbles appeared in the left atrium after a considerable delay. The finding, though ambiguous, was interpreted as being caused by either pulmonary venous return of microbubbles or generation of an ultrasound contrast effect within the left atrium. A 24 hour postoperative study on the intensive care unit (contrast study and oxygen saturations) showed an important leakage. At reoperation residual communications were identified and subsequently closed. At present only the combination of colour flow mapping, multiple contrast studies, and sampling for oxygen saturations seems to be of value for the reliable exclusion of shunting after the creation of total cavopulmonary connections. Paediatric transoesophageal probes or "fingertip" probes that allow imaging and colour flow mapping studies from the lateral and posterior aspects of the right atrium may solve some of the difficulties of obtaining complete information after this type of operation. To date, however, our experience with these techniques in the intraoperative monitoring of Fontan procedures is limited.

Assessment of blood flow patterns and flow velocities by pulsed wave Doppler allows the immediate exclusion of flow obstruction within the Fontan circulation. Immediately after a direct atriopulmonary connection was established pulsed wave Doppler echocardiography showed biphasic, bidirectional pulmonary blood flow. The biphasic nature of blood flow showed that both the atrial contraction and the left ventricular relaxation contributed to pulmonary blood flow[15 16] in these patients. In two of three patients in whom the right ventricular chamber was incorporated into the Fontan circulation the pulmonary artery blood flow was greatest during ventricular systole. This finding showed right ventricular augmentation of pulmonary blood flow immediately after bypass, which may be beneficial in the early postoperative period, as was suggested in earlier studies.[17-19] In the third patient, who had extensive resection of muscular trabeculations between the outlet and the trabecular portions of the right ventricle, pulsed wave Doppler examination did not show a ventricular contribution to pulmonary blood flow. Under these circumstances, and especially when the right ventricle is small, it may become functional some time after repair.

Intraoperative ultrasound provides the surgeon with detailed information on the immediate results of the repair because it can detect slight flow disturbances. It does not measure their haemodynamic importance, however, and this can be misinterpreted. After adequate volume replacement residual obstruction of the outflow tract or interventricular shunting are readily identified. Whereas their severity is often overestimated, the severity of atrioventricular valve regurgitation is more likely to be underestimated when compared with follow up studies. Findings immediately after bypass must be interpreted against the background of the complexity of the pre-existing anomaly and the method of repair. The surgeon must decide whether or not residual haemodynamic lesions need further revision during a second period of bypass. Three of the five patients with documented residual lesions had immediate revision and in all of them the surgical results were good. Studies after bypass and just before closure of the chest in 15 patients and after early reoperation in one patient showed good surgical results in 14. Precordial studies performed before hospital discharge and clinical follow up excluded significant residual lesions in all patients who had good surgical results as assessed by the final post-bypass study. One patient who required epicardial pacing for atrioventricular block and in whom mitral regurgitation was increased after the Fontan procedure died soon after operation; thus the early hospital mortality in this series was 6%.

In patients with a Fontan circulation even small residual lesions can be detrimental and thus require immediate surgical intervention. Intraoperative ultrasound is useful in assessing the quality of the Fontan repair and the need for reintervention. Its use may further reduce both the need for reoperation and early hospital mortality. In addition, the immediate detection and revision of residual lesions should improve functional results in the longer term.

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Factors influencing the persistence of shunting within 24 hours of catheter occlusion of the ductus arteriosus

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Abstract

Catheter occlusion of the persistent ductus arteriosus recently became clinically available with a Rashkind (USCI Bellerica, Massachusetts, USA) umbrella occluder system. A few patients, however, had residual left to right shunting after the procedure. The impact of soaking the foam of the device in a thrombin solution to enhance clotting and of using a device with a diameter of 12 or 17 mm was assessed in 117 consecutive patients undergoing catheter closure. The frequency of residual shunting detected by colour flow Doppler 24 hours after the procedure was the same whether or not thrombin was used.

Several reports have shown the clinical safety and efficacy of transcutaneous occlusion of the persistently patent ductus arteriosus by the Rashkind prosthesis (USCI Angiographics, Bellerica, Massachusetts, USA).[1-3] Successful closure was reported in 0–35% of attempted occlusions.[4-6] The wide difference is attributable to: (*a*) different methods of assessing shunting (auscultation and pulsed or colour Doppler echocardiography), and (*b*) the interval between occlusion and assessment. A recently completed study suggested some technical modifications intended to enhance the rate of complete occlusion.[5] Our study attempts to define those factors or interventions that may influence ductal shunting after placement of the device. To control for those haemodynamic and vascular variables that with time may influence occlusion we choose as our end point evidence of shunting 24 hours after implantation.

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Patients and methods

One hundred and seventeen patients (mean (SD) age 4·0 (3·7) years; weight 15·8 (9·5) kg) had a ductal occluder successfully implanted between February 1986 and June 1989. They were divided into two groups: group 1 with residual ductal shunting and group 2 without residual shunting as determined by pulsed or colour flow Doppler echocardiography, or both, 24 hours after implantation.[7] Details of the procedure have been given before.[3-5] No heparin was administered. Transvenous placement was accomplished in all study group patients.[2] Ductal morphology and the smallest diameter at the junction with the pulmonary artery were determined from the lateral projection of an arteriogram of the descending aorta obtained by injection of contrast into the transductal catheter; arterial catheterisation was not performed.[8] All the ducts occluded were haemodynamically restrictive. A 12 mm occluder was used if the ductus was $<3·5$ mm and a 17 mm occluder was implanted if the ductus was larger, up to a diameter of 9 mm. For the first 62 patients the device was immersed in physiological saline before being loaded on to the delivery catheter. In the remaining 55 patients the occluders were soaked in a solution of topical thrombin (250 IU/ml) for 10 minutes as suggested by Wessel *et al.*[5] We carefully flushed the lumen of the delivery catheter with the thrombin solution to avoid it being diluted on the foam. In the later series, four patients had Doppler evidence of residual shunting within the first 10 minutes after implantation and in these patients an 8 French balloon tipped angiocatheter was inflated in the main pulmonary artery and placed against the pulmonary artery arms of the occluder. We stiffened the catheter with the firm end of a 0·035 inch guide wire (Cook, Bloomington, Illinois) which was inserted to the tip of the catheter but not beyond.[5] Pressure was applied for 10 minutes, and it was monitored by colour Doppler echocardiography to ensure absence of flow. Doppler echocardiographic studies were repeated after we retracted the balloon. We used pulsed and/or colour Doppler echocardiography to assess residual left to right shunting 24 hours after implantation. Groups 1 and 2 were compared by Student's t, χ^2, and the Fisher's exact tests as appropriate.

Results

Thirty nine (33%) (group 1) of the 117 patients had residual shunting one day after the procedure. In 16 of these patients the ductus was closed with a 17 mm occluder and in 23 with a 12 mm occluder. In the 78 patients without residual shunting (group 2) 64 patients had a 12 mm device and 14 a 17 mm device. The use of the 17 mm occluder was significantly associated with the presence of a residual shunt a day after the procedure ($p = 0·007$) and, as was expected, with the presence of a larger ductus: 3·3 (1·1) mm in group 1 *v* 2·7 (0·8) mm in group 2 ($p < 0·01$).

There were 17 instances of residual shunting in the last 55 patients in the series, in whom topical thrombin was used. In the group in which thrombin was not used 22 patients had residual shunting and 40 patients did not. Residual shunting was no less common after the occluder had been soaked in thrombin solution, however ($p = 0{\cdot}522$). The size of the occluder did not influence the effectiveness of the thrombin ($p = 1{\cdot}0$ for the 12 mm and $p = 0{\cdot}4$ for the 17 mm devices). In four patients we attempted balloon tamponade of the residual flow but shunting persisted when the balloon was withdrawn. Finally, there were no significant associations between ductal morphology, patient age, or weight and persistent shunting.

Discussion

We detected a residual shunt by colour Doppler echocardiography one day after the procedure in a third of our patients; in most only a soft systolic murmur was audible.[7] Though long term studies that used colour Doppler echocardiography to assess the success of the procedure detected residual shunts in 10% of patients 1–2 years later, it is not clear which factors influence closure of the duct and could be modified. Because several uncontrolled variables (for example, haemodynamic effects and cellular or vessel ingrowth) may lead to occlusion in the medium and long term, our study attempted to define those variables that may influence closure rates in the first day. It seems that patient selection by age or weight alone has no impact.

Wessel *et al* suggested that soaking the umbrella foam in a solution containing thrombin might increase the rate of successful transcatheter closure.[5] Our data do not support this assertion; we found no improvement in initial closure rates in the group in which we used thrombin. Nor did occluder size influence shunting rates. In a few patients we used a balloon-tipped catheter to stop blood flow through or over the device. Though the balloon catheter stopped flow past the occluder, the shunt persisted, unmodified after the balloon was withdrawn. There is no evidence that the device can be repositioned by this technique, but halting flow through the foam to allow blood stasis and clotting may have some advantages and deserves further study.

We found that implantation of the 17 mm occluder and the size of the ductus were associated with residual shunting. The problem may be intrinsic to a larger ductus or to the way the prosthesis sits within it. The surface area of the foam available to the 17 mm device may not be sufficient to occlude the larger ductal communications, though the diameter of the device arms appears adequate for safe placement.

The Rashkind system is a safe and successful method of eliminating shunts.[5–7] Subtle design changes may further increase both the short and long term success rates. There is enough clinical experience with the procedure for it to be regarded as the first choice for treating patients in whom a ductus arteriosus persists.

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Pulmonary blood flow after total cavopulmonary shunt

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Abstract

The pattern of pulmonary blood flow was studied in three patients after a total cavopulmonary shunt procedure. Doppler studies showed a phasic pattern of flow which varied with the respiratory cycle. Pulmonary blood flow was increased with normal inspiration, and was much augmented by the Mueller manoeuvre. This suggests that flow was occurring when a negative intrathoracic pressure was generated. During a brief Valsalva manoeuvre blood flowed away from the lungs. With a sustained Valsalva manoeuvre there was no spontaneous forward flow; instead there was low velocity pulsatile pulmonary blood flow that coincided with ventricular systole. Left ventricular cavity dimensions decreased, reflecting a considerably reduced pulmonary blood flow.

Pulmonary blood flow after the total cavopulmonary shunt operation is critically dependant on changes in intrathoracic pressure. This has important implications in terms of the immediate postoperative management of these patients.

The total cavopulmonary shunt procedure was first performed by Kawashima and coworkers.[1] It is usually performed in patients with isomerism of the left atrial appendages and complex intracardiac abnormalities which preclude a biventricular repair. Abnormalities of systemic venous drainage are common in these patients; there is usually no intrahepatic portion of the inferior vena cava and systemic venous blood from the lower body drains to a superior vena cava via an azygos or hemiazygos vein.[2] Anastomosis of the superior vena cava (or venae cavae) to the pulmonary arteries thus provides a "physiological" correction of the circulation. Unlike the Fontan procedure and its modification, however, the right side of the heart is completely bypassed, with only venous blood from the coronary sinus and liver draining directly to the atria. Thus pulmonary blood flow occurs without the direct influence of a pumping chamber between systemic veins and pulmonary artery. Despite the uniqueness of this circulation, there is little known about the pattern of pulmonary blood flow in these patients.[3]

We used Doppler echocardiography to show the pattern of pulmonary blood flow at rest. We also examined how changes in intrathoracic pressure induced by the Mueller and Valsalva manoeuvres affected this pattern.

Patients and methods

Three patients were studied. The table shows the full sequential diagnosis, details of previous surgery, and anthropometric data for each patient. There was left atrial isomerism with complex intracardiac anomalies precluding a biventricular repair in all of the patients. Two had undergone previous aortic-to-

Full sequential diagnosis, anthropometric data, and details of previous surgery for each of the patients

Data	*Patient 1*	*Patient 2*	*Patient 3*
Sex	Female	Female	Female
Date of birth	July 1983	June 1977	February 1976
Atrial situs	Left atrial isomerism	Left atrial isomerism	Left atrial isomerism
Systemic venous drainage	Hemiazygos continuation to left superior vena cava. Separate right superior vena cava	Azygos continuation to right superior vena cava Left superior vena cava to innominate vein	Azygos continuation to right superior vena cava Separate left superior vena cava
Atrioventricular connection	Double inlet right ventricle (common valve)	Double inlet left ventricle (common valve)	Double inlet left ventricle (common valve)
Ventriculoarterial connection	Double outlet right ventricle, pulmonary atresia	Double outlet left ventricle, pulmonary atresia	Concordant
Previous procedures	Modified left Blalock-Taussig shunt, right Glenn anastomosis	Classic right Blalock-Taussig shunt	Pulmonary artery banding, left Glenn anastomosis
Date of total cavopulmonary anastomosis	May 1986	February 1989	April 1990
Follow up	4 years	15 months	3 months

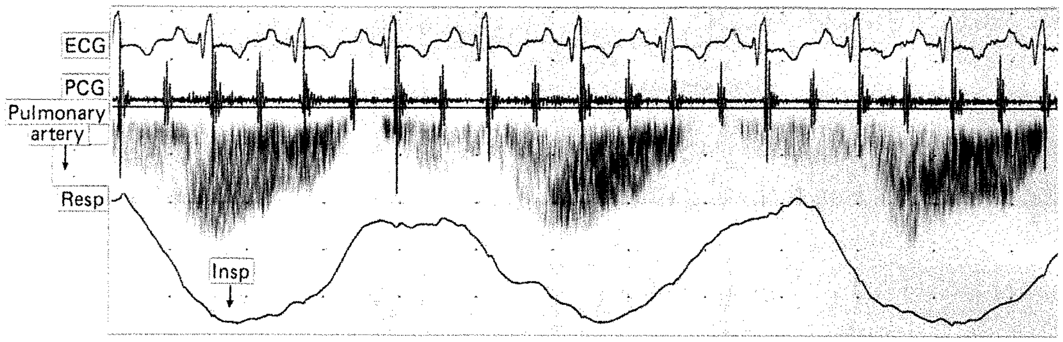

Figure 1 Pattern of pulmonary blood flow in one of the patients during normal spontaneous respiration. Blood flow was synchronous with respiration, increasing on inspiration. ECG, electrocardiogram; PCG, phonocardiogram; resp, respiratory motion trace; insp, inspiration. Velocity calibration interval 12·5 cm/s.

pulmonary shunt procedures; the other had had banding of the pulmonary artery (patient 3). Patients 1 and 3 had also undergone a bidirectional Glenn procedure (anastomosis of a separately draining superior vena cava to the contralateral pulmonary artery) before completion of the total cavopulmonary shunt. In none of the patients was there an intrahepatic portion of the inferior vena cava. The hepatic veins and coronary sinus drained directly to the right sided left atrium in all.

The postoperative course was uncomplicated in all of the patients. The mean hospital stay was nine days. At follow up all patients gave a history of mild cyanosis on exertion but were otherwise symptom free. All patients had normal atrioventricular synchrony with a normal PR interval on the resting electrocardiogram. The axis of the P wave was suggestive of an ectopic atrial focus in all of the patients, however, as is commonly the case in patients with left isomerism.

DOPPLER ECHOCARDIOGRAPHY

All patients were studied with a 5 MHz range gated pulsed wave Doppler imaging system (Toshiba Instruments). They were examined at least three hours after their last meal. Recordings were made with the patient lying at 45° with the neck slightly extended. Suprasternal cross sectional images of the cavopulmonary anastomosis were first obtained to ensure the smallest angle of incidence between blood flow and Doppler beam. Pulsed wave Doppler flow measurements were then recorded with the sample volume at the junction of the superior vena cava with the pulmonary artery in each patient. This site was chosen because flow in this region was laminar and the site of the anastomosis has a relatively fixed cross sectional area. Thus changes in velocity can be assumed to represent changes in the volume of flow. In the two patients in whom both superior venae cavae were anastomosed separately, Doppler recordings were taken in the caval vein to which the azygos vein was connected. Doppler flow-velocity profiles were first recorded during spontaneous respiration and during held end tidal expiration. The patient was then asked to breathe through a mouthpiece that was connected to a valve which allowed rapid occlusion of the airway. The airway pressure was measured by an analogue pressure gauge (Bourdon Instruments), which could be seen by the patient. Doppler flow recordings were then made during several respiratory manoeuvres:

(*a*) Brief Valsalva manoeuvre—that is, intermittent forced expiration (at normal end tidal inspiration) with an open glottis but a closed airway, to a peak airway pressure of 25 cmH_2O. Repeated after 3–5 seconds.

(*b*) Prolonged Valsalva manoeuvre—procedure as above, but the patient encouraged to maintain airway pressure at approximately 25–35 cmH_2O for 20 seconds.

(*c*) Brief Mueller manoeuvre—that is, intermittent forced inspiration (at normal end tidal expiration) with open glottis but a closed airway, to reach a negative airway pressure of -25 cmH_2O, followed by release. Repeated after 3–5 seconds.

(*d*) Prolonged Mueller manoeuvre—as above, with the patient encouraged to maintain negative airway pressure of 25–35 cmH_2O for 20 seconds.

In patients 2 and 3 we recorded an M mode echocardiogram of the left ventricle during a prolonged Valsalva manoeuvre. Cavity dimensions were measured from a parasternal

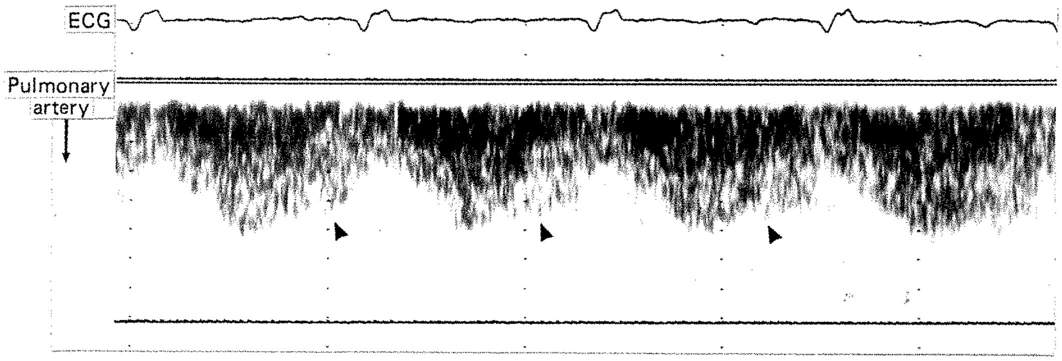

Figure 2 Doppler recording of pulmonary blood flow at held end tidal expiration showing a biphasic pattern. Flow towards the lungs was increased during both ventricular and atrial systole (arrows mark onset of flow coinciding with atrial systole). ECG, electrocardiogram. Velocity calibration interval 12·5 cm/s.

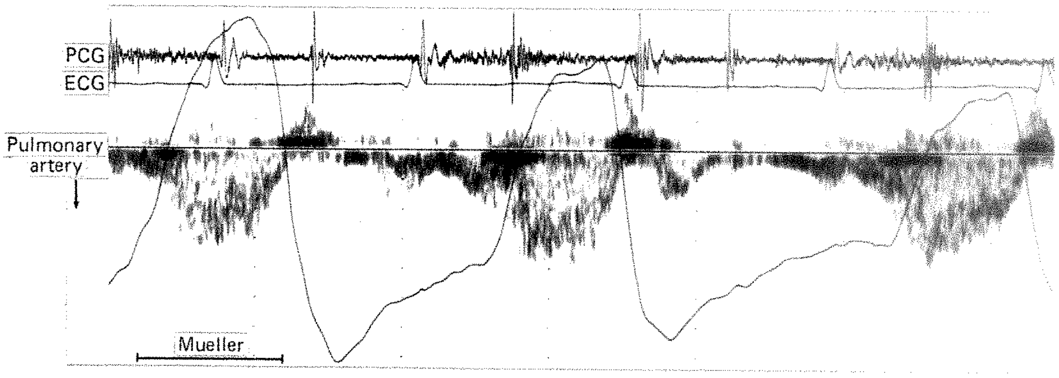

Figure 3 Recording of pulmonary blood flow during repeated brief Mueller manoeuvres in another patient. There was considerable augmentation of blood flow during the manoeuvres. In this patient inspiratory motion registered as an upward deflection on the respiratory motion trace. ECG, electrocardiogram; PCG, phonocardiogram. Velocity calibration interval 12·5 cm/s.

long axis section recorded at the level of the atrioventricular valve tips. Doppler inflow velocities across the common atrioventricular valve were also recorded at rest and during a prolonged Valsalva manoeuvre in these two patients. All measurements were made with a simultaneous electrocardiogram, phonocardiogram, and respiratory motion trace and recorded on paper at a speed of 50 or 100 mm per second.

Results

The patterns of flow at rest and the effect of Mueller and Valsalva manoeuvres were similar in all of the patients.

NORMAL SPONTANEOUS RESPIRATION

Figure 1 shows the effect of normal respiration on pulmonary blood flow. There was a phasic variation of flow velocity that was synchronous with respiratory movements. With inspiration there was considerable augmentation of flow towards the lungs. At end inspiration (at the onset of active expiration) there was cessation of flow towards the lungs in two of the patients (fig 1) and considerable attenuation of flow in the other. During normal resting respiration there was no discernible influence of cardiac contraction on the pattern of pulmonary blood flow in any of the patients. The respiratory variation in flow was lost at held end tidal expiration. In one of the patients there was continuous low velocity non-phasic flow. In the other two patients the flow pattern could be related to the cardiac cycle. In one there was an increase in flow velocity during ventricular systole, and in the other there was a biphasic pattern with an increase in flow velocity coincident with both ventricular and atrial systole (fig 2).

EFFECT OF THE MUELLER MANOEUVRE

Figure 3 shows the effect of repeated brief Mueller manoeuvres in one of the patients. There was considerable augmentation of flow towards the lungs during the manoeuvre in all of the patients. With a prolonged Mueller manoeuvre there was an initial surge of blood flow, followed by continuous, non-phasic flow towards the lungs. There was no phasic element to suggest any effect of cardiac contraction.

VALSALVA MANOEUVRE

There was retrograde flow (away from the lungs) in the superior vena cava in all of the patients during the brief Valsalva manoeuvre (fig 4). With the sustained Valsalva manoeuvre the pattern was quite different. Initially the direction of flow was away from the lungs, as in the brief manoeuvre. After 2–5 seconds phasic forward flow (towards the lungs) was established. Figure 5 shows this pattern. There was virtually no spontaneous flow into the pulmonary artery; the only forward flow occurred during ventricular systole. There was no separate diastolic component to forward flow. In each patient there was a surge of flow towards the lungs on release of the Valsalva manoeuvre.

LEFT VENTRICULAR CAVITY DIMENSIONS

Left ventricular cavity dimensions were recorded at rest and during a prolonged Valsalva manoeuvre in two patients. There were similar

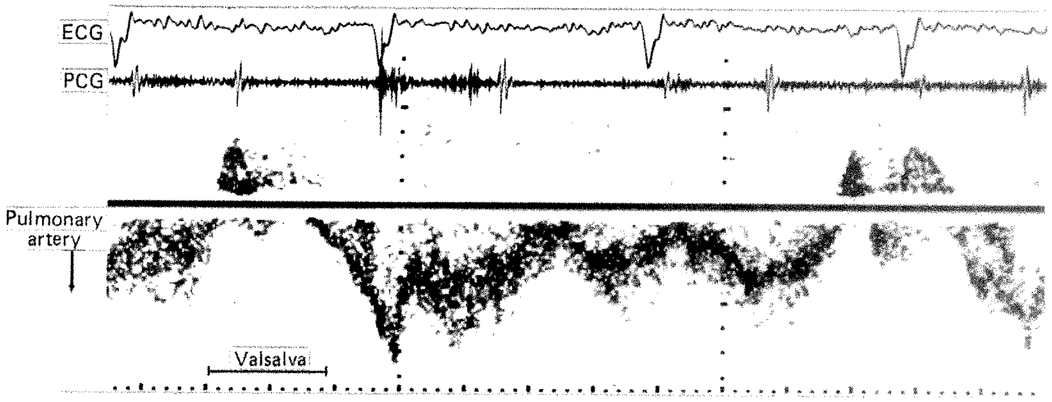

Figure 4 Recording to show the effect of repeated brief Valsalva manoeuvres in patient 1. There was blood flow away from the lungs with each manoeuvre. ECG, electrocardiogram; PCG, phonocardiogram.

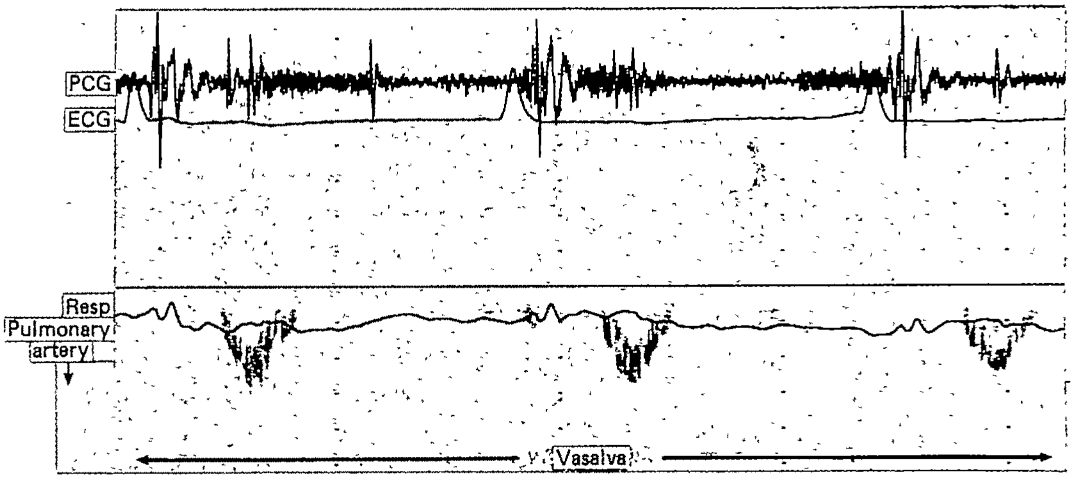

Figure 5 Pulmonary blood flow during a prolonged Valsalva manoeuvre Flow towards the lungs coincided with early ventricular systole. ECG, electrocardiogram, PCG, phonocardiogram; resp, respiratory motion trace. Velocity calibration interval 5 cm/s.

findings in both. Figure 6 shows that the cavity size was much reduced during the prolonged Valsalva manoeuvre in each of the patients. In the patient illustrated there was a dilated cavity with very incoordinate wall motion; cavity dimensions and basal wall motion were normal in the other patient. The end diastolic cavity dimension fell by 7 and 13 mm respectively during a prolonged Valsalva manoeuvre. Doppler inflow velocities recorded across the common atrioventricular valve were reduced in both, suggesting reduced flow. The ratio of the A wave to the E wave was unchanged, however.

Discussion

The total cavopulmonary shunt operation is an extracardiac procedure that provides a physiological "correction" of the circulation in children with complex congenital heart disease. It is usually performed when there is an interrupted inferior vena cava with return of venous blood from the lower body via an azygos or hemiazygos continuation to a superior vena cava. There is usually isomerism of the left atrial appendages with complex associated intracardiac anomalies that preclude a biventricular repair in these patients. Anastomosis of the distal superior vena cava (or venae cavae) end to side with the pulmonary artery thus directs most of the systemic venous return to the pulmonary vascular bed. Unlike the Fontan operation or its modifications,[4 5] the right atrium and ventricle are completely bypassed. There is therefore a unique opportunity to examine the factors that may influence pulmonary blood flow when there is no pumping chamber in the pathway between the systemic veins and the pulmonary artery.

It is clear from our study that respiratory movements have a major influence on pulmonary blood flow in these patients. At rest the flow in the superior vena cava towards the lungs is synchronous with and increased by inspiration. It is likely that the negative intrathoracic pressure generated during normal inspiration draws blood from the systemic venous reservoir towards the lungs. Certainly, this flow is considerably increased during the Mueller manoeuvre, when a much larger negative intrathoracic pressure is generated. When respiration was suspended at end expiration the respiratory variation in pulmonary blood flow, not surprisingly, was lost. In one patient there was continuous low velocity flow with no phasic element. In the other two, however, there was a

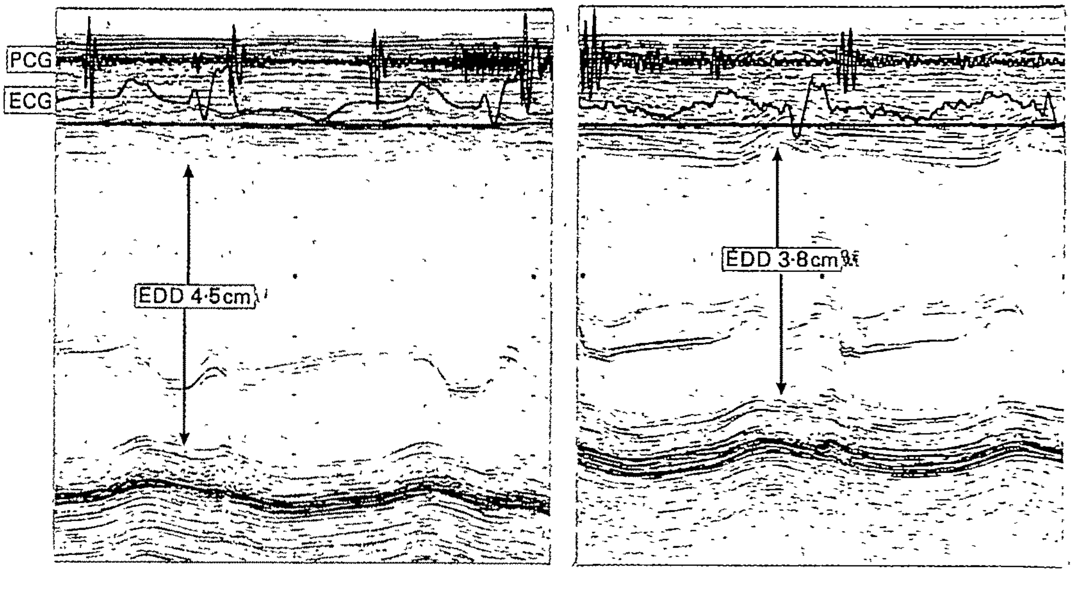

Figure 6 M mode echocardiograms of the left ventricle recorded before (right hand panel) and during (left) a prolonged Valsalva manoeuvre. There was a considerable reduction in cavity dimension as a consequence of diminished pulmonary blood flow (see fig 5). ECG, electrocardiogram; PCG, phonocardiogram; EDD, end diastolic dimension.

phasic variation with the cardiac cycle. Flow towards the lungs occurred predominantly during ventricular systole, but in one of the patients there was a biphasic flow pattern with an increase in flow velocity occurring with atrial systole (fig 3). This latter observation confirms the findings of Miura and coworkers,[3] in the only other study of pulmonary blood flow in these patients. The effect of respiration was not specifically examined, but in their two patients examined after total cavopulmonary shunt operation there was a biphasic pattern of pulmonary blood flow at held end expiration. A biphasic pattern of pulmonary blood flow has also been shown in patients after the Fontan operation.[6 7] Similarly, the effects of respiration have not been specifically examined in these patients, but there is some evidence that pulmonary blood flow increases during inspiration in patients with an atriopulmonary anastomosis.[8 9]

There was an important, and potentially clinically significant, effect of the Valsalva manoeuvre in our patients. With a brief increase in intrathoracic pressure to 25 cmH_2O there was a reversal of flow in the superior vena cava. That is, blood flowed away from the lungs. With the sustained Valsalva manoeuvre, spontaneous blood flow towards the lungs was abolished. There was, instead, a small amount of forward flow with each ventricular systole (fig 6). The considerable reduction in ventricular cavity size during this manoeuvre presumably reflects this reduction in pulmonary blood flow. The exact mechanism responsible for this pattern of flow is unknown, however. It is possible that it reflects the effects of a raised systemic venous pressure with an additional pulsatile element imposed by ventricular systole. Thus there is transmission of the arterial pulse to the venous system which overcomes the effects of the raised intrathoracic pressure—that is, blood is being pushed into the lungs. Alternatively, this pattern may occur as a consequence of a fixed intrathoracic volume. During ventricular systole blood leaves the thorax and so must be replaced, either from the hepatic veins (a limited blood reservoir) or via the systemic veins. We speculate therefore that this flow pattern may reflect physiology similar to that of the x descent of the jugular venous pressure pulse, flow in the pulmonary artery occurring during ventricular systole—that is, the blood is "pulled" into the lungs.

Whatever the mechanism these findings may have important clinical implications. In the immediate postoperative period these patients require positive pressure ventilation during their recovery from operation. It is likely that any increase in mean airway pressure will decrease pulmonary blood flow. Indeed an important reduction in cardiac output with increasing values of positive end expiratory pressure has been shown in patients immediately after the Fontan operation.[10] It is therefore important to maintain the mean airway pressure as low as possible during the postoperative period in these patients. An alternative strategy might be to ventilate these patients with a negative extrathoracic pressure device. Our preliminary data suggest that this mode of ventilation may have two potential advantages. Firstly, the detrimental effects of positive pressure ventilation may be avoided. Secondly, because negative intrathoracic pressure is generated, pulmonary blood flow is augmented.[11]

In summary, pulmonary blood flow in patients after a total cavopulmonary shunt procedure is much influenced by respiratory movements. There is increased flow during normal inspiration, and this is augmented during the Mueller manoeuvre. The Valsalva manoeuvre, by producing a positive intrathoracic pressure, leads to a clinically significant reduction in pulmonary blood flow.

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Analysis of left ventricular wall movement before and after reimplantation of anomalous left coronary artery in infancy

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Abstract

Five infants who underwent direct reimplantation or redirection of an anomalous left coronary artery from the pulmonary artery to the aorta were studied. There were no deaths from the procedure. Anastomoses were patent at a mean follow up of 33 months. Left ventricular angiograms before and after operation were digitised frame by frame. Analysis of wall motion showed considerable generalised hypokinesia with no change in cavity shape before operation. After reimplantation there was a significant improvement of global ventricular function as assessed by ejection fraction and end diastolic shape index. There was also a tendency for the shape index change to increase; this was compatible with better global systolic function. Three of the four patients who were restudied showed normal isometric and contour wall motion plots. One child, the oldest at the time of operation, still showed asynchronous onset of contraction and isovolumic relaxation.

The procedure offers a low risk of mortality and a high rate of patency of the anastomosis. Improvement of ventricular function can be remarkable and its extent cannot be assessed simply by ejection fraction measurements.

Anomalous origin of the left coronary artery from the pulmonary artery is a rare congenital anomaly. Infants presenting with heart failure from impaired left ventricular function have a high mortality and morbidity without operation.[1] It is now clear that establishment of a two coronary artery system is the treatment of choice either by direct reimplantation[2] or by a technique in which the left coronary artery is tunnelled into the aorta via a pulmonary artery baffle and aortopulmonary window.[3 4]

While improvement of global indices of left ventricular function has been documented after operation (for example, an increased ejection fraction), we know of only a few studies[5] of wall movement. An earlier operation may reduce the number of persistent wall motions abnormalities and hence the risk of late sudden arrhythmic deaths if such abnormalities reflect electrical instability[6] at junctions of normal and impaired myocardium.

Patients and methods

From October 1984 to March 1989, five infants with an anomalous left coronary artery arising from the pulmonary artery underwent operation at the Brompton Hospital. They all presented with heart failure and evidence of myocardial infarction or ischaemia on the electrocardiogram. The diagnosis was suspected on echocardiography and confirmed at cardiac catheterisation when selective right coronary artery injection showed late filling of the left coronary system. Preoperative left ventricular angiograms were available in four.

The mean age at operation was 4·2 months (range 2·8–5·7) and mean weight 4·6 kg (range 3·6–5·6). Cardiopulmonary bypass was used in two and deep hypothermia with circulatory arrest in the other three. Direct reimplantation was possible in four while an intrapulmonary pericardial baffle was constructed in the remaining infant.[4]

Cardiac catheterisation and angiography were performed postoperatively in four patients at a mean of 33 months (range 22–40) after the operation. The left coronary artery was selectively injected through a 5F Amplatz or left Judkins catheter. Left ventricular angiograms obtained in the 30° right anterior

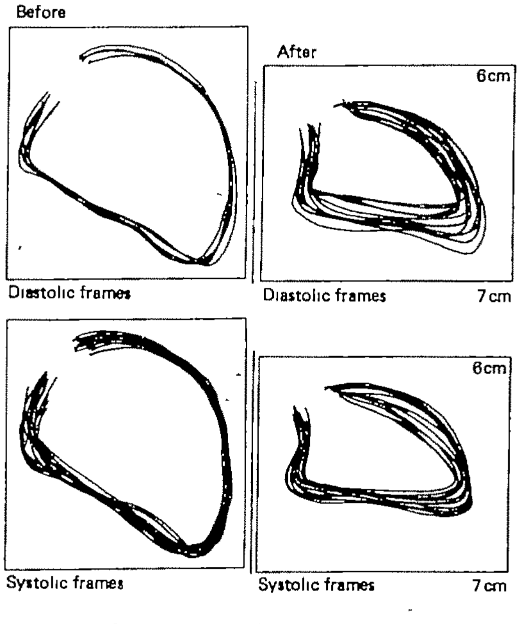

Figure 1 Cavity outlines obtained from patient 4 in systole and diastole before and after reimplantation. There was global improvement in the amplitude of wall motion.

Values derived from frame by frame analysis of left ventricular angiograms

Patient	Age at operation (mnth)	EF (%)		EDSI (%)		Shape index change (%)	
		Before	After	Before	After	Before	After
1	4·7	18	—	87·5	—	0	—
2	4·0	22	74	85	81	5	13·5
3	5·7	23	40	92	77	0	5
4	2·8	21	70	89	81	7	13
5	3·8	—	69	—	77·5	—	16
Median		21·5*	69·5*	88·2*	79*	2·5†	13·5†

Mann-Whitney U test: *p < 0·03, †NS EDSI, end diastolic shape index; EF, ejection fraction.

oblique view were digitised frame by frame to study abnormalities of wall movement before and after operation.[7] Plots of superimposed cavity outlines were obtained in systole and diastole (fig 1). The cavity area was calculated by numerical integration, and volumes, derived from the area (area-length method[8]) were used to calculate ejection fraction. The left ventricular shape index, a measurement of the "roundness" of the cavity outline, was derived from single plane angiograms as 4π(cavity area)/(perimeter)^2. The maximum shape index is 1, or 100%, when the cavity outline is circular, and cavity obliteration gives a value of zero. The shape index of the normal left ventricle decreases by approximately 20% during systole.[9] Thus a substantial part of ejection can be accounted for by the change in cavity shape alone, rather than global myocardial shortening.

Plots of local wall movement were displayed against time. The left ventricular cavity outline was divided into 40 equal segments at end diastole. The wall position in each frame was then measured in mm along a line defined for each of these segments to the nearest point on the end systolic outline. Wall movement was displayed to give a three dimensional impression (isometric wall motion plot), where inward movement was an upward deflection, or as a series of contour lines joining points which had the same displacement (contour wall motion plot). Successive contours represent inward or outward movements of 1 mm. The two vertical lines show times of minimum cavity area and mitral valve opening.[7] Onset of inward motion is marked "X" for each segment.[10]

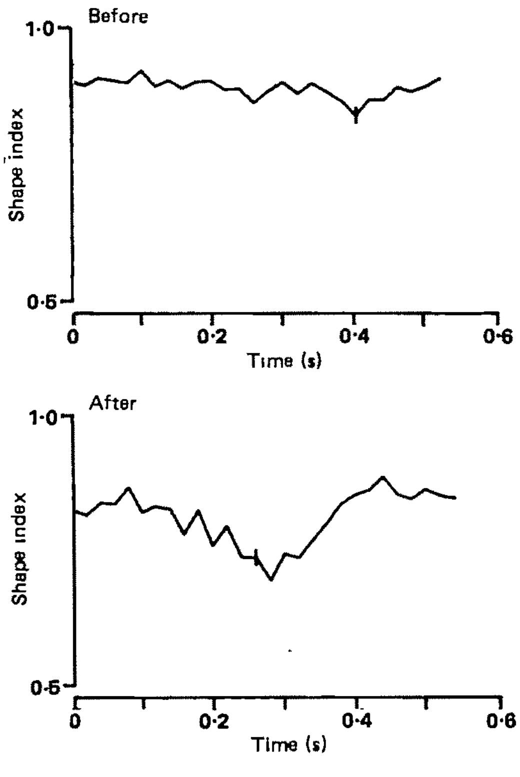

Figure 2 Plots of shape index obtained from patient 4. Before operation the cavity was more circular at end diastole (time = 0 s), and there was little change in cavity shape during the cardiac cycle. After reimplantation the degree of systolic shape change had increased suggesting improvement in global systolic function.

Results

PATENCY OF ANASTOMOSIS

The four patients who were re-evaluated had direct reimplantation of the anomalous coronary artery into the aorta. All anastomoses were patent at a minimum follow up time of 22 months. The remaining patient who underwent repair via an intrapulmonary baffle showed clinical improvement one year later and the state of the anastomosis will be assessed at the end of a longer follow up. This infant had a baffle type of repair because the origin of the left coronary artery was a sheath of small vessels arising from the pulmonary artery.

GLOBAL LEFT VENTRICULAR FUNCTION

The table shows the indices of global left ventricular function. The ejection fraction was severely impaired (median 21·5%) before operation but returned to normal in all but one patient (median 69·5%) after operation. The left ventricular cavity (fig 2) was more circular than normal at end diastole (greater end diastolic shape index) and showed a lesser degree of change in shape during systole (lower systolic index change). The end diastolic shape index decreased after operation ($p < 0·03$) and there was a tendency for the degree of systolic shape change to increase; both features are compatible with improved global systolic function (fig 2).

LOCAL WALL MOVEMENT

The very low amplitude of wall movement seen preoperatively made it difficult to analyse regional wall motion in isometric and contour wall motion plots. Similar plots after operation showed a considerable improvement of the pattern of wall motion (figs 3–5). Plots were considered to be within normal limits in three of the four patients who were recatheterised. Shape changes were normal with synchronous onset of inward motion (marked with X for each segment) in all of these patients and there was no evidence of pathological asynchrony during isovolumic relaxation (figs 3 and 4). In the remaining child there were residual abnormalities. Figure 5 shows the isometric and contour plots from this patient. The onset of inward motion was delayed in the anterior region. Furthermore, outward motion of segments in the inferior region began before mitral valve opening—that is, during isovolumic relaxation. This child was the oldest one in this series at the time of operation (5·7 months).

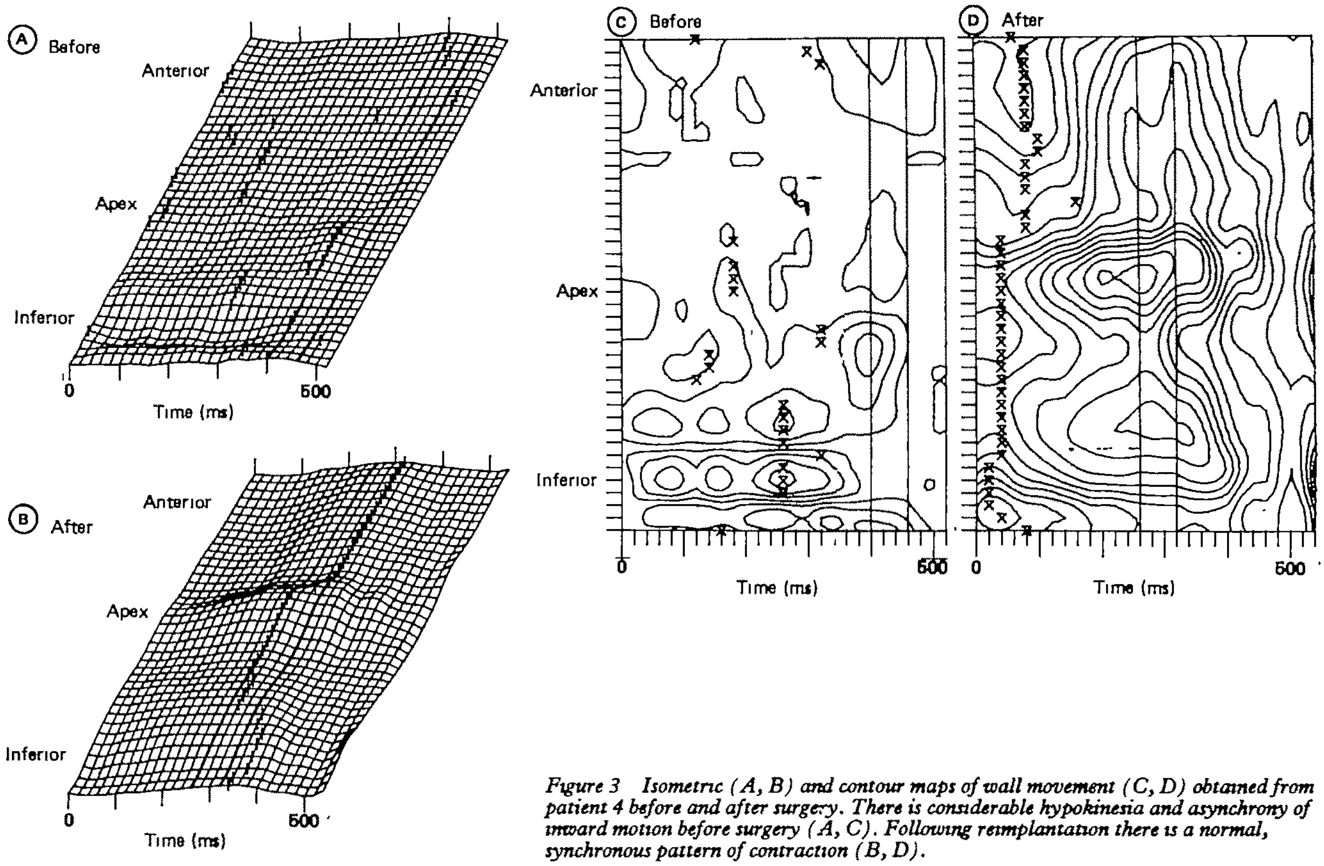

Figure 3 Isometric (A, B) and contour maps of wall movement (C, D) obtained from patient 4 before and after surgery. There is considerable hypokinesia and asynchrony of inward motion before surgery (A, C). Following reimplantation there is a normal, synchronous pattern of contraction (B, D).

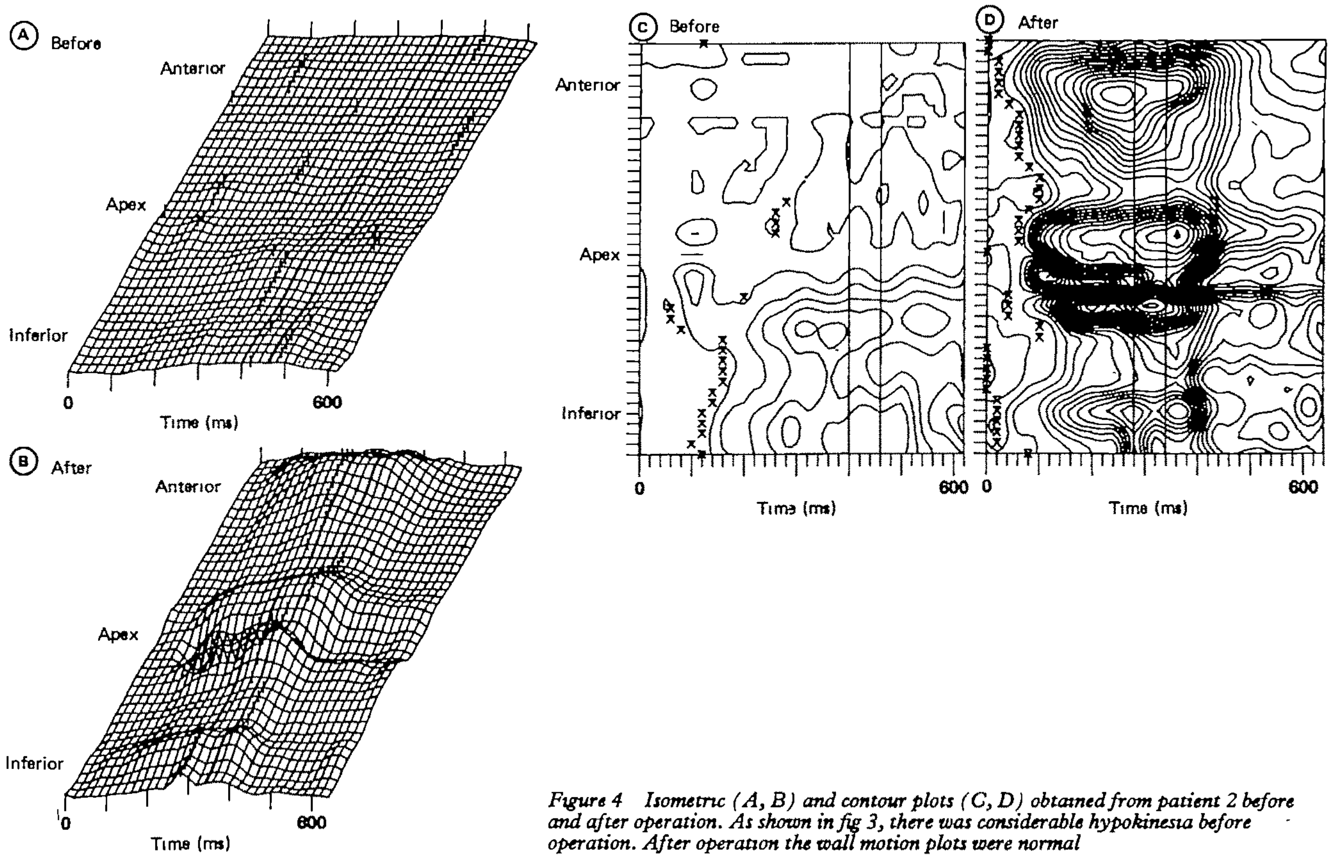

Figure 4 Isometric (A, B) and contour plots (C, D) obtained from patient 2 before and after operation. As shown in fig 3, there was considerable hypokinesia before operation. After operation the wall motion plots were normal

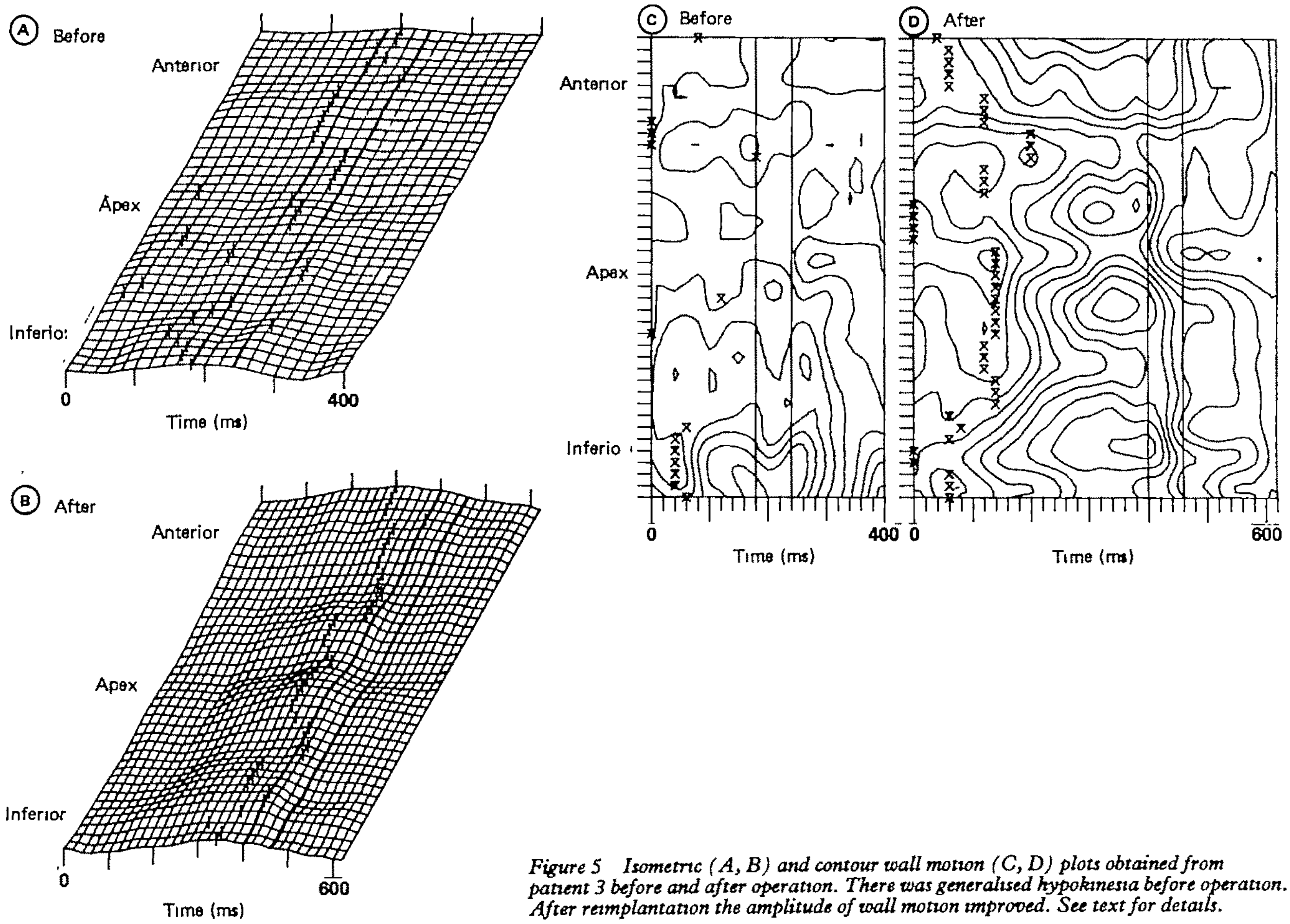

Figure 5 Isometric (A, B) and contour wall motion (C, D) plots obtained from patient 3 before and after operation. There was generalised hypokinesia before operation. After reimplantation the amplitude of wall motion improved. See text for details.

Discussion

Reported surgical mortality for an anomalous coronary artery in infancy in the early 1980s was as high as 75–80%[11 12] and a delay of operation was therefore advocated.[11]

With new techniques of obtaining a dual coronary artery system either by direct reimplantation or redirection of the coronary artery, the chances of early survival have improved.[13 14] In our series there was no operative mortality, as in other recent series.[5 15 16] The high patency rate of the anastomosis in the patients who underwent direct reimplantation also supports the use of this technique even for very sick and young infants. Early surgical intervention with establishment of a dual coronary artery system now seems to be the best option for infants with symptoms.[15 17 18]

In 1980, Levitsky *et al* reported one case of improvement of ejection fraction, assessed by echocardiography, after reimplantation of the anomalous coronary artery into the aorta.[19] There was also evidence of improved contraction,[16] ejection fraction,[15 18] and shortening fraction[17] after restoration of a dual coronary artery system early in life. Rein and colleagues in 1987[5] reported improvement in regional and global function assessed by echocardiography before and after the use of Takeuchi's technique[5] in five infants. Preoperatively they did not find localised abnormalities of ventricular function but rather a uniform reduction of the shortening fraction for various segments studied with no segment-to-segment variation.

Analysis of global left ventricular function in four of our patients after operation showed a similar considerable improvement of global systolic function in all patients. Not only did the ejection fraction increase but the normal change in left ventricular shape reappeared. Local wall movement became normal in timing and extent in three patients, and in one child residual localised hypokinesia and asynchrony persisted during isovolumic relaxation. Despite this, the ejection fraction increased strikingly and the child is now symptom free. This child was the oldest at the time of operation and while no firm conclusions can be drawn about the optimal timing of operation, it seems reasonable to suggest that the earlier the operation is performed the greater the chance of myocardial recovery and return to a normal systolic function.

There can be no doubt that early reimplantation or redirection of an anomalous coronary artery is the best treatment for infants with symptoms. It is attended by a low mortality, has a high rate of anastomotic patency, and dramatically improves left ventricular function. Whereas our data on left ventricular function confirm the previously published data, the demonstration of full recovery of regional ventricular function in our patients is unique. Synchronous contraction returns, reflecting normal interrelations between the various functional units of the ventricular myocardium. Presumably therefore, they were not lost even though the cavity was dilated and the amplitude of endocardial motion was greatly reduced. There is further support for recommending direct reimplantation wherever possible.

Longer term follow up is obviously required, but short and medium term results are already encouraging and indicate longer survival and a better quality of life for these children.

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Br Heart J 1991;65:223–4

CASE REPORTS

Ebstein's anomaly associated with splenomegaly and reversible hypersplenism

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Abstract

A case of Ebstein's anomaly associated with chronic right heart failure, hepatosplenomegaly, and the haematological features of hypersplenism is presented. The haematological abnormalities were corrected after tricuspid valve replacement but recurred with the reemergence of clinical features of right heart failure.

Ebstein's anomaly often results in right heart failure with an increase in systemic venous pressures. The latter, when transmitted as raised portal venous pressures, can cause splenomegaly and the haematological features of hypersplenism. The occurrence of reversible hypersplenism associated with changes in right sided pressures in Ebstein's anomaly has not been described before.

Case report

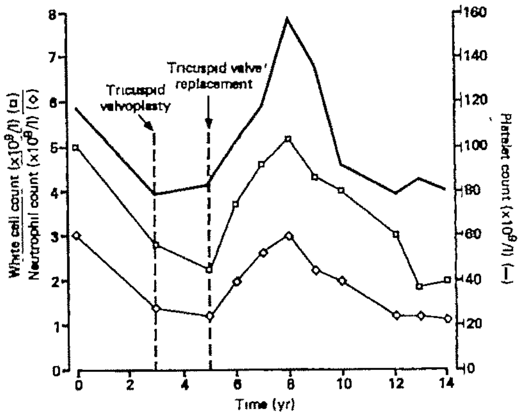
Ebstein's anomaly was diagnosed in a child with cyanosis on exertion, characteristic physical findings, and radiological evidence of cardiomegaly. He remained well, however, without treatment, until the age of 35 when he presented with dyspnoea and epistaxis. On examination he had cyanosis at rest, features of right heart failure with tricuspid regurgitation, hepatosplenomegaly, and widespread purpura. Investigations performed at that time showed a haemoglobin concentration of 188 g/l (normal range 135–165), white cell count of 3·0 × 10^9/l (normal range 4·0–11·0 × 10^9/l), and a platelet count of 75 × 10^9/l (normal range 150–450 × 10^9/l). Cardiac catheterisation showed raised right sided pressures and tricuspid regurgitation (table) and normal left sided pressures. At operation, undertaken on the basis of symptoms and evidence of heart failure, the tricuspid valve was shown to be incompetent with an aneurysmally dilated right atrium, small right ventricle, and a patent foramen ovale. The tricuspid valve insertion was typical of Ebstein's anomaly. Initial surgical intervention was plication of the right atrium, which made the tricuspid valve competent, together with closure of the foramen ovale. However, there was little improvement in symptoms after this operation. Right heart failure became worse over the next two years and he required further admissions. Investigations at this time showed a haemoglobin concentration of 175 g/l, a fall in his white cell count to 2·2 × 10^9/l, and a platelet count of 70 × 10^9/l. Cardiac catheterisation showed a further increase in his right sided pressures (table) and another operation was considered.

Pressure recordings (systolic/diastolic (mm Hg)) at cardiac catheterisation before each operation and 16 years after replacement of the tricuspid valve

Chamber	*Before valvoplasty*	*Before tricuspid valve replacement*	*16 years after tricuspid valve replacement*
Right atrium	11/1 (mean = 6)	30/15 (mean = 24)	33/20 (mean = 27)
Right ventricle	22/0 (mean = 12)	30/15 (mean = 23)	57/20 (mean = 39)

The tricuspid valve was replaced with a Starr-Edwards prosthesis two years after valvoplasty and his clinical signs of right heart failure resolved with a considerable improvement in symptoms. This was associated with a dramatic reduction in his hepatosplenomegaly as assessed clinically and on abdominal radiography and a sharp rise in his neutrophil and platelet counts, which restored them to normal (figure). Between 1978 and 1989 signs of right heart failure gradually reemerged with progressive hepatosplenomegaly and concomitant falls in his neutrophil and platelet counts (figure). Cardiac catheterisation showed a further increase in right sided pressures (table).

At each admission the patient was investigated for causes of his pancytopenia. Bone marrow samples showed a consistently hypercellular marrow, with increases in all cell



White cell, neutrophil, and platelet counts during each operation and at follow up. (Means of three observations.)

lines, but no evidence of megaloblastosis, dysplasia, or infiltration. Intravascular haemolysis was excluded by a normal peripheral blood film, serum haptoglobin, and urinary haemosiderin. Coombs test and the Ham acid lysis test were negative and serum vitamin B_{12} and folate concentrations were normal. Anti-DNA antibodies and the rheumatoid arthritis latex test were negative. Infective endocarditis was excluded by repeated negative blood cultures. The pancytopenia was therefore attributed to hypersplenism. An ultrasound scan of the abdomen confirmed hepatic venous congestion and hepatosplenomegaly, and the presence of splenic varices implied portal hypertension, though the portal vein was patent and of normal size.

Discussion

Hypersplenism is defined as a depression of one or more of the cell counts in the circulating blood that can be wholly attributed to splenic enlargement and is associated with a cellular bone marrow.[1] Other causes of pancytopenia: hypersplenism, marrow aplasia/dysplasia, marrow infiltration, megaloblastosis, systemic lupus erythematosis, and paroxysmal nocturnal haemoglobinuria were excluded as indicated above. The patient's initial polycythaemia is usual in cases of Ebstein's anomaly with right to left shunt,[2] and was corrected by closure of the shunt.

Our patient with Ebstein's anomaly had had chronic right heart failure with raised systemic venous pressures for many years. Chronic right heart failure with hepatic venous congestion is associated with splenomegaly in 12–25% of patients[3-5]; the mechanism is believed to be portal venous hypertension secondary to raised hepatic venous pressures. Moderate to severe symptoms in Ebstein's anomaly or the presence of heart failure are regarded as indications for tricuspid valve plication or replacement.[6] Replacement has been shown to reduce right atrial pressures,[6] and should therefore reduce both systemic and portal venous pressures. Reduction in portal venous pressures, for example after distal spleno-renal shunting procedures, reversed the neutropenia and thrombocytopenia of hypersplenism and this was associated with a reduction in splenic size.[7 8]

Hypersplenism in our patient seems to be the result of raised systemic (and thus portal) venous pressures, and treatment of the cardiac lesion with reduction in these pressures improved the secondary haematological characteristics. Such an association between Ebstein's anomaly and hypersplenism has not been described before; perhaps because detailed longitudinal studies over many years are often not possible. Our patient is also unusual because he has survived 17 years after the onset of heart failure—a poor prognostic sign in patients with Ebstein's anomaly.

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Br Heart J 1991;**65**:225–6

Balloon dilatation of pacemaker induced stenosis of the superior vena cava

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Abstract

A 53 year old woman with symptomatic pacemaker associated superior vena cava syndrome was treated successfully with balloon angioplasty. She was well six months after the procedure.

The superior vena cava syndrome is a well recognised but unusual complication of permanent pacemaker implantation. The syndrome results from the development of a stenosis in the superior vena cava with symptoms arising secondary to impaired regional venous drainage. Management is controversial and thoracotomy and caval reconstruction have been used to relieve symptoms.[1 2] We report the successful use of balloon angioplasty as the primary treatment of this condition.

Case report

A 53 year old woman presented with a long history of severe palpitation. Atrioventricular nodal reentrant tachycardia was confirmed at electrophysiological study. The arrhythmia was refractory to medical treatment and in 1985 a PASAR (Telectronics) antitachycardia pacemaker was implanted. A Telectronics atrial lead was advanced to the right atrial appendage without difficulty. This relieved her symptoms considerably. A year after the procedure she presented with pleuritic chest pain and treatment with warfarin was started after a clinical diagnosis of pulmonary embolism. In 1988 she developed swelling of her hands and face and an angiogram showed stenosis of the superior vena cava proximal to its entry into the right atrium. Pulmonary artery pressure was normal and a pulmonary angiogram showed no evidence of pulmonary embolism. No action was taken. By 1990 the swelling of her upper body, which was especially severe in the morning and was made worse by activity, had increased and in addition she was experiencing worsening headaches. There was mild pitting oedema of the arms. The jugular vein was non-pulsatile and visible beyond the angle of the jaw. The electrocardiogram showed minor repolarisation abnormalities and the chest *x* ray was normal. Computed tomography showed a normal mediastinum. A repeat angiogram of the superior vena cava showed that the stenosis was more severe than before (fig 1). There was a gradient of 9 mm Hg between the superior vena cava above the stenosis and the right atrium. The angiographic appearance was suggestive of a fibrotic stricture with no evidence of associated thrombus. Contrast injections into the cephalic vein in the left antecubital fossa showed another stenosis at the junction of the brachiocephalic and the subclavian veins on that side. Multiple collaterals were also present. Balloon angioplasty of the stenosis of the superior vena cava was undertaken. A 0·035 inch straight guide wire and 7F Gensini catheter were introduced from the right femoral vein and the wire was passed through the stenosis to the right subclavian vein. The catheter was then advanced through the stenosis to allow a 0·035 inch exchange J guide to be introduced. The stenosis was then dilated with an 8 mm balloon catheter initially and then with a 10 mm balloon catheter (Mansfield). A good angiographic result was obtained (fig 2) and the gradient across the stenosis was abolished. The procedure was uneventful apart from two brief episodes of supraventricular tachycardia, during which the pacing unit continued to function normally. On examination the next day the jugular vein was no longer visible above the sternal angle. She remained symptom free six months after the procedure.

Discussion

Though venous abnormalities induced by pacemaker leads are common,[3] stenosis of the superior vena cava and associated symptoms are unusual. The condition is more common

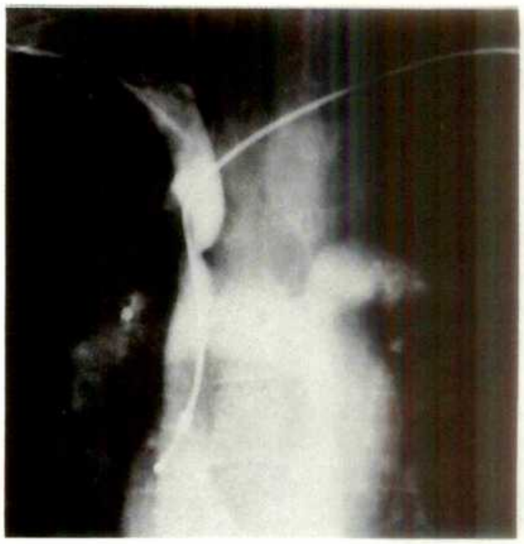

Figure 1 Dye injection into the right subclavian vein showing stenosis of the the superior vena cava above its junction with the right atrium. The Teletronics atrial lead can be seen in position.

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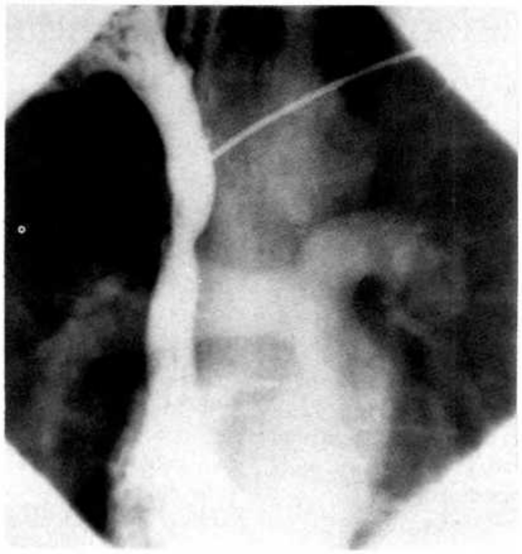

Figure 2 Angiogram after balloon dilatation showing considerable improvement in flow.

in patients with retained leads and in those with infectious complications after pacemaker implantation[1] and is the result of thrombosis, which may be associated with fibrosis. Ideal management is not established but thrombotic occlusion may be reduced by the administration of intravenous thrombolytic agents. Several patients have been given oral anticoagulants but the risk of resultant cerebral haemorrhage is probably increased by coexistent cerebral venous hypertension.[4,5] Thoracotomy and caval repair have also been undertaken when symptoms persisted and a stenosis was shown on angiography. There are reports of the use of percutaneous balloon angioplasty in two previous patients. In one it was used in conjunction with thrombolytic treatment[6] and in the other for restenosis after caval repair in which a pericardial patch was inserted.[1]

Our patient is the first in whom balloon dilatation was used successfully as a primary treatment for stenosis of the superior vena cava: a stenosis of an innominate vein has been dilated and reported previously.[7] The stenosis that we dilated seemed to be fibrotic, and not associated with thrombus; it may have resulted from damage at the time of introduction of the pacing lead. The angioplasty technique we used was standard and no appreciable problems were encountered. We expect that any complications are likely to be those associated with vascular access, lead displacement, and caval rupture. Restenosis has been reported[1] but the likely incidence cannot be determined from the available reports.

Because the risk of cerebral haemorrhage is likely to be increased by the use of anticoagulants we recommend balloon angioplasty as the primary treatment for fibrotic strictures occurring in this unusual condition. Thrombolytic agents should be used only when coexistent thrombus is visible on angiography and they should be used with caution.

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Diagnosis of mitral valve aneurysm by transoesophageal echocardiography

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Abstract

In a patient with mitral valve aneurysm precordial echocardiography suggested a mistaken diagnosis of infective endocarditis. Transoesophageal echocardiographic examination established the correct diagnosis, which was subsequently confirmed at operation. Transoesophageal echocardiography gives better resolution of lesions associated with the mitral valve than precordial examination and may improve the diagnostic accuracy.

True aneurysms, or diverticulae, of the mitral valve are a rare cause of mitral regurgitation. They are most common in patients with infective endocarditis affecting the aortic valve,[1–7] but they may also present with chronic mitral regurgitation,[8] or as a complication of mitral valve prolapse.[9] The precordial echocardiographic features of mitral valve aneurysms are non-specific,[5 8 10] and can be misinterpreted as a large vegetation, cystic left atrial myxoma, or degeneration in association with a prolapsing leaflet. Delay in making the correct diagnosis increases the risk of infection, embolisation, or rupture of the aneurysm; these complications can be prevented by surgery to repair or replace the valve.[5] We report a patient in whom a mitral valve aneurysm was diagnosed by transoesophageal echocardiography.

Case report

A 43 year old woman was admitted to hospital with a purpuric rash. On direct questioning she also gave a six month history of night sweats. She did not report any previous cardiac history. Multiple sclerosis had been diagnosed three years earlier after two separate presentations with neurological symptoms, both of which resolved completely with steroid treatment. She was not on any long term drug treatment. No cardiac murmurs had been noticed on previous hospital visits.

We found several purpuric skin lesions on her trunk and upper limbs. There were no other peripheral signs of infective endocarditis and her temperature, pulse, and blood pressure were normal. A loud pansystolic murmur (grade 3) was present at the apex.

The haemoglobin concentration, white cell count, and platelet count were normal as was a full coagulation screen. Six blood cultures were negative, as were serological tests for a wide range of viruses. Chest radiography and electrocardiography were normal. Precordial echocardiography showed a mass attached to the posterior leaflet of the mitral valve that was thought to be a large vegetation. Colour flow Doppler examination showed moderately severe mitral regurgitation. Infective endocarditis was diagnosed and treatment with an intravenous antibiotic was started. She was subsequently referred to the Western Infirmary for further cardiological assessment.

In systole a transoesophageal echocardiographic examination showed a large cystic lesion in the left atrium attached to the posterior leaflet of the mitral valve (fig 1). In diastole the cyst collapsed and became much less prominent (fig 2). Colour flow mapping

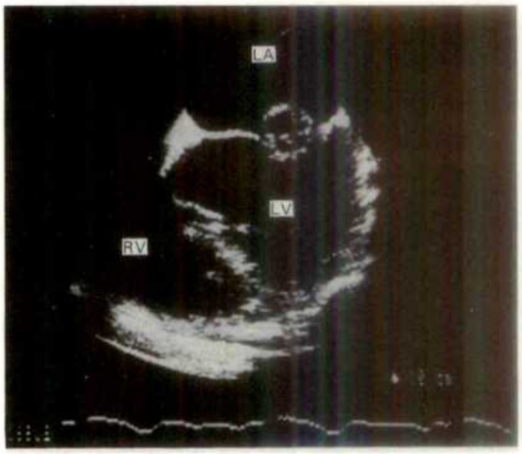

Figure 1 Transoesophageal echocardiogram in systole showing a large aneurysm on the mitral valve. LA, left atrium; LV, left ventricle; RV, right ventricle

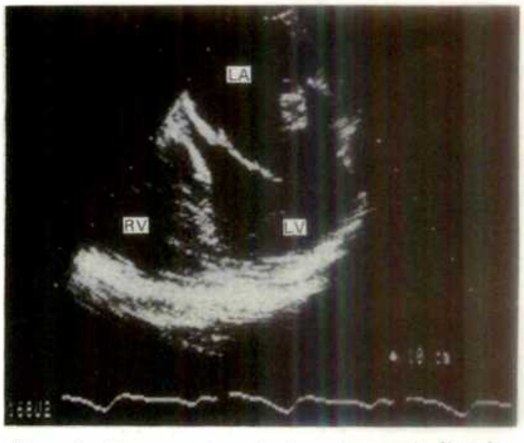

Figure 2 Transoesophageal echocardiogram in diastole showing collapse of the aneurysm and its origin on the posterior leaflet. LA, left atrium; LV, left ventricle; RV, right ventricle

showed an eccentric jet of mitral regurgitation directed towards the interatrial septum. Cardiac catheterisation with left ventriculography subsequently confirmed that this lesion was a mitral valve aneurysm that communicated with the left ventricular cavity. The cyst was excised on cardiopulmonary bypass, and the posterior leaflet of the mitral valve was repaired without the need for valve replacement.

Discussion

Aneurysm of the mitral valve is more commonly reported as a complication of infective endocarditis affecting primarily the aortic valve.[1-7] In other reports,[8] as in our patient, there was no previous history of endocarditis, though a subclinical infection cannot be excluded. Aneurysms of the mitral valve seem to be more common on the anterior leaflet than the posterior mitral.[1,2]

Diagnosis of mitral valve aneurysm by precordial cross sectional echocardiography has been reported before.[2,3,5-9] Our patient, however, shows that precordial echocardiography may not be diagnostic in this condition and can be misleading especially when the posterior leaflet is affected.[8-10] Mitral valve aneurysm may be confused with cystic degeneration of the valve, a cystic atrial myxoma, or a large vegetation.[10] Transoesophageal echocardiography can distinguish between these conditions. Because the oesophagus lies immediately behind the left atrium it provides an excellent echocardiographic window and allows a high ultrasound frequency to be used. This gives much better resolution of abnormalities in the region of the mitral valve than precordial echocardiography.[11] We are aware of only one previous report of transoesophageal echocardiographic diagnosis of a mitral valve aneurysm, where the findings resembled those in our patient.[10]

Aneurysm of the mitral valve should be considered in the differential diagnosis of mass lesions seen on the atrial side of the mitral valve at precordial echocardiography. A transoesophageal examination may be needed in such patients. When the characteristic features described above are present a diagnosis of mitral valve aneurysm can be made without recourse to cardiac catheterisation.

We thank Dr John Reid and Mr Alan Faichney for permission to report this case.

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Br Heart J 1991;65:229–30

Recognition of pacemaker lead infection by transoesophageal echocardiography

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Abstract

Transoesophageal echocardiography identified a pacemaker lead infection in a patient in whom transthoracic echocardiography was negative and there were no specific signs of skin inflammation over the pulse generator.

Infection of a permanent pacemaker system is defined as one or more of the following: (*a*) local inflammation and abscess formation in the pulse generator pocket; (*b*) erosion through the skin of part of the pacing system that is followed by secondary infection; (*c*) fever associated with positive blood cultures in a patient without a focus of infection elsewhere.[1] Diagnosis can sometimes be difficult, especially when the pacemaker leads are infected without local inflammation of the pulse generator pocket and without erosion of part of the pacing system. Transthoracic echocardiography can sometimes be helpful but image resolution is often inadequate.

We found that transoesophageal echocardiography was useful in the diagnosis of infection of the pacemaker leads in one of our patients.

Case report

In March 1986 a 47 year old man was admitted for the first time to another hospital for surgical correction of an atrial septal defect. He was readmitted in June 1986 because of syncope caused by an atrioventricular block, Mobitz type II, and a dual chamber pacemaker was implanted. Four days after implantation of the pacemaker system, discrete inflammation appeared near the pulse generator and treatment with local disinfection and oral antibiotics (tetracyclines) was started. Forty eight hours later the inflammation had disappeared.

In November 1988 the patient was treated for septicaemia caused by *Staphylococcus capitis*, bronchopneumonia, and spondylodiscitis of L2 and L3. The patient was treated with oxacillin for six weeks. Slight tenderness was noted over the pulse generator pocket. After the normal antibiotic treatment, there was normal healing of the pulse generator pocket and no inflammation. Computed tomography showed the beginning of organisation of the spondylodiscitis lesion.

The patient presented in March 1989 with tenderness over the pulse generator. Examination showed discrete inflammation without evidence of abscess formation. The pulse generator was removed but the pacemaker leads were left in place. A new pacemaker system with new atrial and ventricular leads was implanted on the contralateral (left) side.

The patient was readmitted in July 1989 with fever and chills. Both the old and new pacemaker pockets showed normal healing without inflammation. Leucocytosis (white cell count 20 × 10^9/l with 87% neutrophils) and considerable evidence of inflammation (erythrocyte sedimentation rate was 106 mm/h, fibrinogen was 600 mg/dl) were detected. Three blood cultures were positive for *Staphylococcus capitis*. Transthoracic echocardiography showed no evidence of infection of the pacemaker leads. The patient was treated with antibiotics but two days after intravenous administration was changed to oral treatment, fever reappeared and again three blood cultures grew *Staphylococcus capitis*.

The patient was referred to our hospital for transoesophageal echocardiography. Four pacemaker leads were detected in the superior vena cava and right atrium. We also saw what appeared to be a large (2 cm–1 cm), mobile and lobulated vegetation (figure) alongside one or more of the leads. Because of this we decided to remove all the parts of the pacemaker.

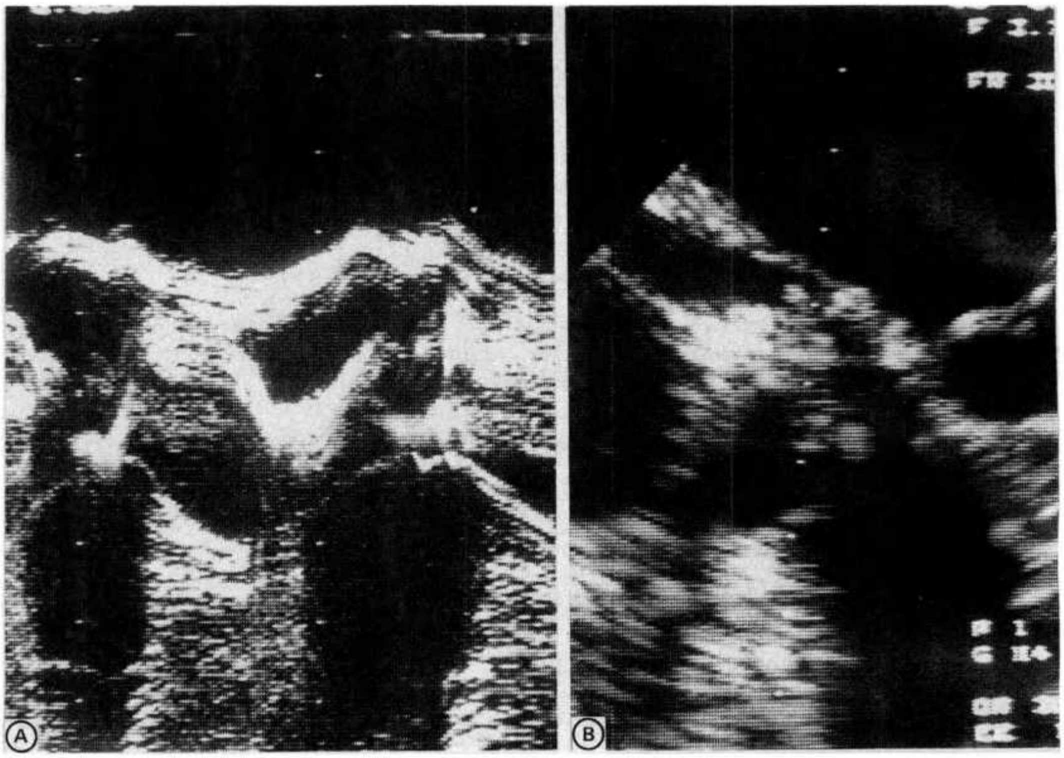
The right atrium was opened to remove the four electrodes which were cut as high as possible in the superior vena cava. We found a large vegetation on an atrial lead. This lay along the wall between the tricuspid valve and inferior vena cava. The patches used to correct the atrial septum defect and the tricuspid valve were intact. A new pacemaker system was inserted: a pulse generator was implanted in the epigastric region and two electrodes were implanted on the epicardium, one at the base of the right atrium and the other on the right ventricle. Then the right pectoral leads and the left pectoral leads and left pulse generator (surrounded by an old haematoma) were removed.

At follow up four months later the patient was well, free from fever, and had no signs or symptoms of infection or inflammation without antibiotic treatment.

Discussion

Pacemaker infection is unusual. The reported incidence ranges from 0% to 12·6%[2]; with current pacemaker procedures the infection rate ranges from 0·8% to 3%.[1 3 4] The number of patients at risk of infection will increase as permanent pacemakers become more widely used.

This potentially lethal condition sometimes has a slow course and causes little pain. When there are no clear signs of infection and the



Transoesophageal echocardiogram ((A) M mode and (B) cross sectional) showing pacemaker lead with vegetation in the right atrium.

pacing system has not eroded the skin, diagnosis of pacemaker system infection can be very difficult. This is often the case when intermittent treatment with antibiotics is given—as in our patient.

The leads often become infected in cases of pacemaker infection: pacing electrodes from 88% of patients operated for pacemaker infection gave positive cultures.[1] This, however, is difficult to demonstrate preoperatively. Transthoracic echocardiography is not sufficiently sensitive. We found that transoesophageal echocardiography was helpful in our patient. We found only one report on the diagnosis of hidden pacemaker lead sepsis by transoesophageal echocardiography.[5] Larger studies will be needed to assess the sensitivity and specificity of transoesophageal echocardiography in the diagnosis of pacemaker lead infection.

When there is a strong suspicion of pacemaker infection we recommend the replacement of the pulse generator and leads. Treatment with antibiotics alone is not sufficient and can mask the progression of the infection.[1]

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Low energy catheter ablation of right ventricular outflow tract tachycardia

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Abstract

A 38 year old woman with a structurally normal heart presented with near syncope and had right ventricular outflow tract tachycardia. She was intolerant of antiarrhythmic medication and underwent low energy catheter ablation. Six non-arcing shocks of 25 J were delivered to the right ventricular outflow tract. No further ventricular tachycardia occurred during a follow up of seven months without antiarrhythmic treatment.

Ventricular tachycardia of left bundle branch configuration and with an inferior axis in patients with structurally normal hearts is recognised as a clinical syndrome.[1-3] It is usually brought on by stress and exercise and normally has a good prognosis.[1] Unlike most ventricular tachycardia, it can be suppressed by treatment with β blockers and calcium channel blockers. These features are consistent with a catecholamine sensitive focus arising from the right ventricular outflow tract. Experience with surgery and catheter ablation in this condition is limited.

We describe a patient with right ventricular outflow tract tachycardia and a structurally normal heart who was intolerant of antiarrhythmic medication and in whom low energy catheter ablation was successful.

Case report

CLINICAL PRESENTATION

A 38 year old woman was referred because of two episodes of near syncope that occurred on exertion. She had also experienced several episodes of dizziness lasting a few seconds, without noticeable palpitation. She complained of dyspnoea but she could climb 20 stairs. She smoked 20 cigarettes per day. Clinical examination was entirely normal. The electrocardiogram at rest and chest *x* ray were normal. Echocardiography showed normal chamber sizes and normal valves. Radionuclide ventriculography at rest was normal for both ventricles. Magnetic resonance imaging showed normal left and right ventricular dimensions, wall thickness, wall thickening, and ejection fractions.

She performed the modified Bruce protocol on a treadmill. Before she mounted the treadmill her heart rate increased to 100 beats/minute and she developed frequent unifocal ventricular extrasystoles with a left bundle branch configuration and inferior axis (fig 1). After two minutes and 45 seconds of stage I she developed frequent bouts of non-sustained ventricular tachycardia (cycle length

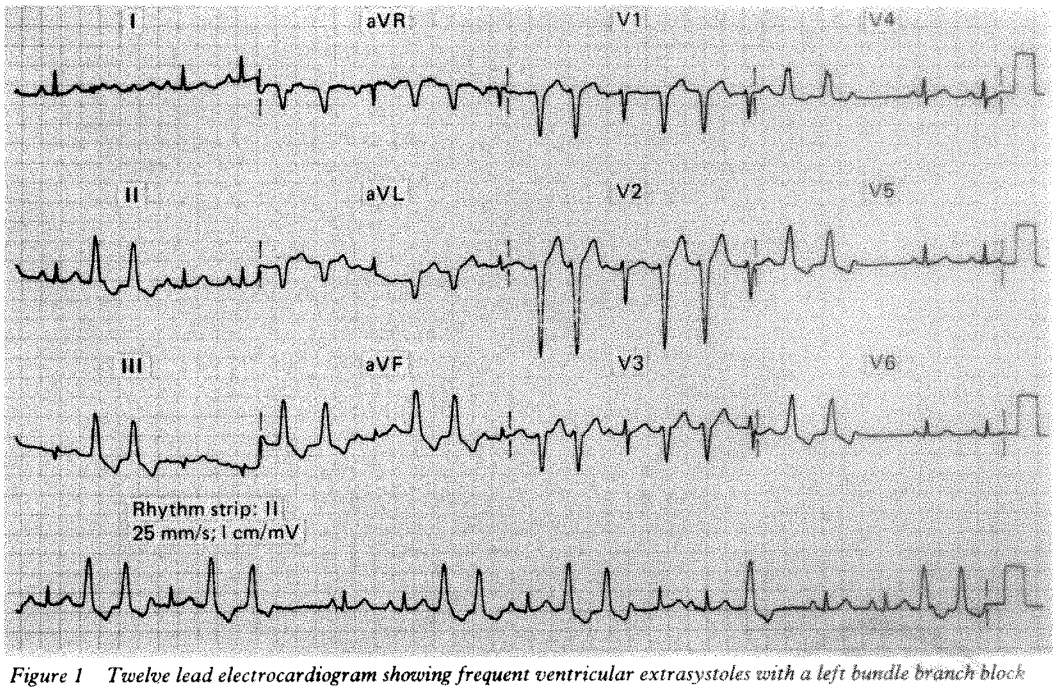

Figure 1 Twelve lead electrocardiogram showing frequent ventricular extrasystoles with a left bundle branch block and inferior axis configuration.

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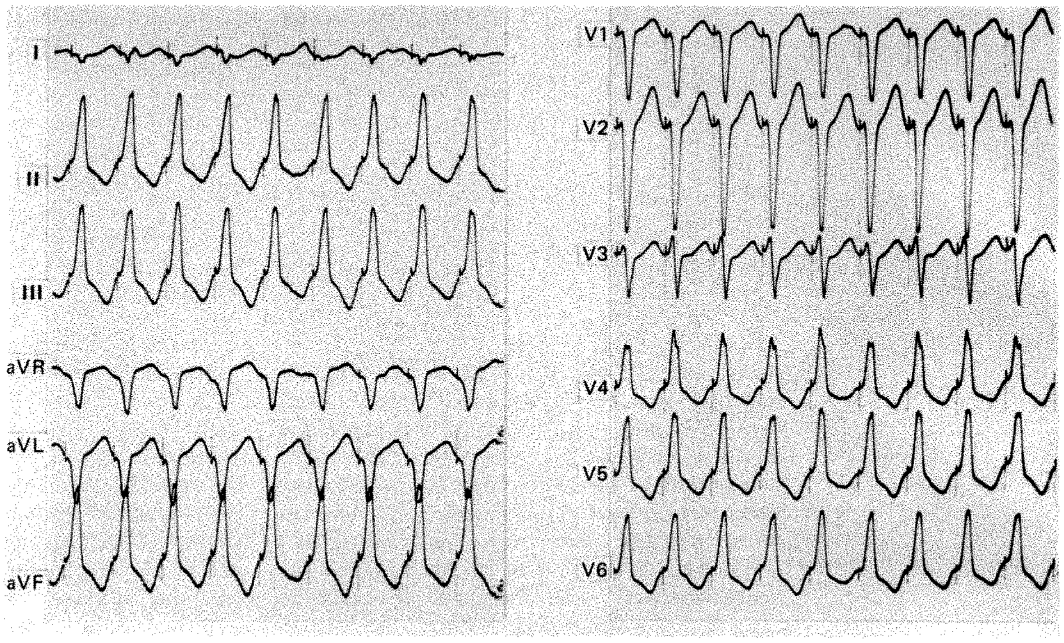

Figure 2 Twelve lead electrocardiogram produced by pacing at the ablation site. The configuration of the QRS complexes closely matched that of the ventricular extrasystoles in fig 1.

380 ms) with the same configuration as the previous extrasystoles. She felt unwell and the test was stopped. The episodes of ventricular tachycardia rapidly ceased but she continued to have single ventricular extrasystoles for six minutes. After her admission to hospital a repeat exercise test was performed. Again she developed frequent unifocal extrasystoles with a similar configuration before she mounted the treadmill. This time she exercised for 55 seconds into stage III before sustained ventricular tachycardia developed (cycle length 380 ms). She was given intravenous lignocaine and after 20 seconds the rhythm reverted to sinus tachycardia. She was subsequently treated with sotalol but was intolerant of this.

ELECTROPHYSIOLOGICAL STUDY

Episodes of up to 20 beats of ventricular tachycardia occurred spontaneously during isoprenaline infusion and the duration of ventricular tachycardia was very sensitive to the dose of isoprenaline. Programmed electrical stimulation did not induce the ventricular tachycardia even when isoprenaline was infused. Pacemapping from the right ventricular outflow tract produced complexes that resembled the clinical tachycardia.

Because the tachycardia was sensitive to isoprenaline, we prescribed further β blockade with metoprolol. The episodes of dizziness resolved but she felt ill on this medication. She refused further pharmacological treatment and requested a curative procedure. After detailed discussion she gave her informed consent to catheter ablation; surgical ablation was planned if this failed.

At repeat electrophysiological study we pacemapped from the right ventricular outflow tract using a Josephson quadripolar catheter with 5 mm spacing. We manipulated the catheter until we obtained the best pacemap (fig 2). A contoured ablation electrode[4] was placed at this site. We used a previously described protocol[5] to deliver six shocks of 25 J to both the proximal and distal poles of the ablation catheter at this site with a NHH ablater[4] as the power source and a chest paddle over the left side of the sternum as the cathode. The arrhythmia that followed the delivery of the shocks was transient: ventricular tachycardia lasting five to 15 seconds followed the delivery of shocks three to six. It had a left bundle branch configuration but the frontal axis was different from that of the clinical ventricular tachycardia. This did not have any haemodynamic consequences. After three of the shocks there was transient atrial fibrillation with a controlled ventricular rate and no haemodynamic effects. No further ventricular extrasystoles were seen during the remainder of the electrophysiological study despite further isoprenaline infusion. The patient was monitored on the coronary care unit but no further ventricular extrasystoles or arrhythmias occurred. The patient was discharged home on no medication. Creatine kinase measured at five minutes, and four, eight, 18, and 24 hours rose to a peak of 117 IU/l at eight hours, which is within the normal range for our laboratory.

FOLLOW UP

At review one and seven months after ablation the patient was well. She had no further dizziness, syncope, dyspnoea, or tiredness. Twenty four hour Holter monitoring two weeks and seven months after the ablation showed no ventricular extrasystoles or ventricular tachycardia. At a repeat exercise test a month after the ablation she exercised 10 seconds into stage IV before being limited by fatigue in her legs. Her heart rate at peak exercise was 170 beats/minute and there were no ventricular extrasystoles or ventricular tachycardia.

Discussion

The ventricular tachycardia in this patient was uncharacteristic of that seen with ischaemic heart disease. It was brought on by exercise, stress, and isoprenaline infusion and extrasystoles were not recorded if the heart rate was below 100 beats/minute. It was abolished by metoprolol. This is all consistent with the tachycardia being very sensitive to catecholamine concentration. It was not inducible at electrophysiological study, even when isoprenaline was infused. The failure to induce the tachycardia with programmed electrical stimulation suggests that it was caused by automaticity or triggered activity not reentry.

The site of origin was localised by pacemapping to the right ventricular outflow tract. This is consistent with other reports.[1 2 6] We used an ablation system designed to reduce the delivered energy and barotrauma.[4] We believe that many of the serious side effects seen with conventional ablation are caused by the high energies used and the accompanying large pressure disturbances. These side effects have limited the use of ablation and a recent report of the world registry concluded that the use of ablation in the ventricle remains experimental.[7] Measurements of voltage and current during the delivery of these six shocks showed that impedance remained constant and indicated that arcing had not taken place and therefore that no pressure disturbance had occurred.[8] We suggest that it is particularly important to avoid barotrauma in thin walled structures such as the right ventricle and coronary sinus because of an increased risk of rupture. We believe that the use of this low energy ablation system will improve safety and reduce complications. The lack of rise in serum creatine kinase is also consistent with reduced myocardial damage.

This is the first report of successful low energy catheter ablation of a catecholamine sensitive right ventricular outflow tract tachycardia. Reports of high energy catheter ablation in this condition are rare. Wilber *et al* described a patient in whom two conventional shocks of 200 J were delivered to a site in the outflow tract after an excellent pacemap but in whom ventricular tachycardia returned after several hours. This patient went on to have successful surgical ablation.[6] At surgery the site of earliest endocardial breakthrough was 2 cm lateral to the site of the catheter ablation. Hartzler described, in the first report of catheter ablation for ventricular tachycardia, a patient with successful ablation of right ventricular outflow tract tachycardia; this followed unsuccessful surgical endocardial resection.[9]

In this patient we delivered six low energy shocks. Our previous animal work (unpublished) showed that increasing numbers of low energy non-arcing shocks can produce lesions of similar size to those produced by shocks of much higher energies but without causing dangerous large pressure disturbances. Thus we believe that it is safer to deliver repeated non-arcing shocks than single much larger shocks. Unfortunately, failure to induce the tachycardia immediately after the ablation does not predict success in the next few hours or days because the cells essential to the tachycardia mechanism may be reversibly damaged and not necrotic. Thus at present there is no reliable end point at which ablation can be stopped. In this case ventricular tachycardia was not inducible; but after the first three shocks we saw single ventricular extrasystoles with the same configuration as the clinical ventricular tachycardia. Because we thought that insufficient damage had been produced we delivered three further shocks. After each of these we saw no further extrasystoles with the configuration of ventricular tachycardia.

The report by Wilber *et al*[6] and our report are consistent with this syndrome being caused by a relatively localised abnormal area rather than a diffuse myocardial process. The localised nature of the substrate suggests that this syndrome may be suitable for treatment by catheter ablation in patients intolerant of medication.

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LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Life at a price: the implantable defibrillator

Sir,—Professor Campbell (*Br Heart J* 1990; 64:171–3) outlined some of the dilemmas surrounding the use of the implantable cardioverter-defibrillators (ICDs) and in particular stressed the cost of the device and the lack of established guidelines for selection of patients. We would like to draw attention to some of the data already available to aid cardiologists in this difficult task.

Cost-benefit analysis of ICDs has been attempted by two groups. Kupperman *et al* defined a group of patients with out-of-hospital cardiac arrest caused by haemodynamically unstable ventricular tachycardia or ventricular fibrillation occurring in the absence of acute myocardial infarction,[1] all of whom subsequently had persistently inducible ventricular tachycardia or fibrillation despite serial drug testing. She then collected data on the implantation and follow up costs of the ICD and compared them with the costs for drug treatment of the same group. The ICD cost $17 400 per life-year saved. This was based on the performance of the ICDs available in 1986; the development of programmability, a five-year ICD life, and transvenous insertion techniques were estimated to bring the annual cost down to $7400. There are many assumptions involved in the calculation of such figures but they are of similar order of magnitude to the costs of heart transplantation ($26 900 per life-year) and the treatment of severe hypertension in men aged 40 years ($11 100 per life-year).

Buxton *et al* performed a similar analysis using 1990 costs in the United Kingdom and produced a range of estimates from £6000 to £20 000 per life-year saved (the lower cost assumes a reduction in ICD price and the cost of implantation, an increase in ICD life and the cost of amiodarone treatment, and a higher incidence of death in the untreated group).[2]

We believe that it would be sensible for the development of defibrillator use in Britain to be centred around the identification of those patients most likely to benefit from defibrillator implantation and evaluated against the current best treatment for these groups. Concentration of defibrillator implantation in a small number of centres would maximise the potential for systematic assessment.

To illustrate the importance of patient selection we have used Buxton's cost estimates in several scenarios It should be stressed that there are potentially very large margins of error in these figures which are costed assuming an ICD life of two years and which take no account of any economic contribution made by the patient during this period. Their main purpose is to illustrate the relative cost of using the ICD within different groups. Data from Wilber *et al* stratifying survival after out-of-hospital cardiac arrest[3] enable calculation of the cost of ICD use based on the inducibility of arrhythmia at electrophysiological study, suppression of the arrhythmia by drug treatment, and left ventricular function (low EF = ejection fraction ⩽ 30%). This represents the non-prophylactic use of the ICD.

Patient group	*Cost per life-year saved*
Inducible, suppressed, high EF	Dubious benefit
Non-inducible, high EF	£110 000
Inducible, suppressed, low EF	£68 000
Inducible, non-suppressed, high EF	£24,000
Non-inducible low EF	£21 000
Inducible, non-suppressed, low EF	£16 000

In the same way the prophylactic use of the implantable defibrillator in post-infarction patients can be costed. Survival data from the St George's Hospital post-infarction database produce the following figures:

All post-infarction patients	£442 000
Patients with ejection fraction <40%	£220 000
Patients with positive late potentials, reduced heart rate variability, and more than 10 extrasystoles per hour	£35 400

In conclusion, we believe that with current data it is possible to identify patients likely to benefit most from implantation of an ICD. Most of these patients are not at present referred for assessment at specialist centres. We should encourage such referral and at the same time strive to establish funding for a programme of assessment at several designated implantation centres. Only in this way will reliable, sensitive, and rapid evaluation be achieved.

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1 Kupperman M, Luce BR, McGovern B, *et al.* An analysis of the cost-effectiveness of the implantable defibrillator. *Circulation* 1990; 81·91–100.
2 Buxton MJ, O'Brien BJ, Rushby JA *Cost-effectiveness of the automatic implantable cardioverter defibrillator: a preliminary assessment.* (Health Economics Research Group Research Report No 7.) Uxbridge: Brunel University, 1990
3 Wilber DJ, Garan H, Finkelstein D, *et al.* Out-of-hospital cardiac arrest· use of electrophysiological testing in the prediction of outcome. *N Engl J Med* 1988;318·19–24

Electrical neurostimulators for pain relief in angina

Sir,—The editorial on electrical neurostimulators for relief of angina (*Br Heart J* 1990;63:141–2) was a timely recognition of the benefit of this form of treatment. The various forms of electrical neurostimulation, be it carotid sinus stimulation, electro-acupuncture, transcutaneous electrical nerve stimulation (TENS), or dorsal column stimulation, all seem to work via a combination of analgesia and suppression of sympathetic activity.

There is no evidence that any type is more efficacious than the other. There is, however, an enormous difference in cost and patient morbidity. The dorsal column stimulator device is expensive and insertion of the electrodes requires epidural implantation. Invasive procedures and insertion of devices are associated with pain and suffering. These devices can lead to continuing discomfort, and there is the risk of infection and device malfunction, requiring operative intervention. The costs include the dorsal column stimulator unit (leads, connection, and pulse generator) at $A5570 (about £2300), two surgical procedures for implantation, testing, and wiring, and approximately three days as an inpatient. In addition, should problems occur, neurosurgical exploration may be required. In comparison, a TENS unit costs between $A100 (£41) and $A300 (£125) depending on sophistication and portability, and is non-invasive. Furthermore, the cost of an acupuncture needle is $A1.

The first patient treated with dorsal column stimulation as quoted in the editorial unfortunately did not have a trial of TENS or acupuncture before the procedure.[1] These may have been equally effective. The patient also had subsequent readmissions to hospital for stimulator malfunction at 3·5 months, 15 months, 24 months, and four years, and required exploration on two occasions.

Recent work by Han suggests the optimal frequency of stimulation for pain relief is probably 15 Hz (personal communication). At this frequency there is stimulation of all three opiate receptors—mu, delta, and kappa—due to release of endorphins, metenkephalins, and dynorphins.[2] A synergistic, not just an additive effect is seen when the three receptors are simultaneously stimulated.[3]

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1 Murphy DF, Giles KR Intractable angina pectoris: management with dorsal column stimulation. *Med J Aust* 1987;146:260
2 Han JS Progress in the pharmacological studies of acupuncture analgesia. In Paton SW, Mitchell J, Turner P, eds *Iuphar 9th international congress of pharmacology, London, 1984 Proceedings volume 1* London: Macmillan, 1984.
3 Huang L, Ren MF, Lu CJ, Han JS Mutual potentiation of enkephalin, dynorphin A-(1–13) and morphine in their analgesic effect in the spinal cord of the rat [Abstract]. In: Han JS, ed. *The neurochemical basis of pain relief by acupuncture. A collection of papers 1973–1987* Beijing Medical University, 1987 281.

This letter was shown to the author, who replies as follows:

Sir,—Dr Colquhoun makes a good point. Transcutaneous electrical nerve stimulation (TENS) is an underrated but effective way of helping angina pain in some patients. We always give our patients a trial of TENS treatment before considering epidural spinal cord stimulation. But it is clear that patients prefer the totally implantable system. TENS systems are bulky, cumbersome, and skin reactions are common. Dr Colquhoun's arguments are similar to those put forward when the external Lucas pacemaker system was used. That was also much cheaper but it was displaced by totally implantable pacemaker systems. There are problems with the present epidural electrodes which slip too frequently; but with further developments it should be possible to overcome these, and we are now trying new designs.

It is not our experience that all forms of electrical neurostimulation are equally effective. Some patients respond better to TENS than epidural stimulation and vice versa. For this reason we now insert a temporary electrode that can remain in place for 2–3 weeks to assess effectiveness before we implant the permanent unit; this also ensures that an expensive unit is not implanted unnecessarily.

Finally, I was interested in Dr Colquhoun's comments about the optimal frequency of stimulation and the work by Han. We have tried stimulating at 15 Hz and it seems to be effective but some patients describe it as a rather unpleasant sensation compared with higher frequency stimulation. But this subject is in its infancy (in the West) and there is much to explore about mechanisms and the best techniques.

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Limited potential of special ambulance services in the management of cardiac arrest

SIR,—We agree with Dr Rowley and colleagues that there has not been sufficient critical analysis of the effectiveness of ambulance personnel with advanced training (*Br Heart J* 1990;64:309–12). However, we wish to make the following observations about their findings and raise important questions about the development of the emergency ambulance service.

Concentration on those patients with prehospital cardiac arrest brought to the accident and emergency department excludes an unknown number of resuscitation attempts terminated by attending doctors. It may be that crews with defibrillator training spend more time at the scene of an arrest, increasing the likelihood that a general practitioner will arrive, certify that the patient is dead, and release the ambulance. The basic emergency crew will "scoop-and-run", leaving less scope for GP involvement. This may explain why larger numbers of patients were transported to hospital by the crews with a more basic training. What were the total number of resuscitation attempts made by each type of crew, regardless of later hospital transfer?

In our area ambulances only transport victims of cardiac arrest to hospital if resuscitation is in progress. When resuscitation is inappropriate a doctor is called to certify death and the patient is left at the scene or taken to the mortuary. We were surprised therefore that 64 of 147 patients were taken to hospital by defibrillator trained crews without any attempt at resuscitation. These patients had not been pronounced dead by a medical practitioner. What criteria did the ambulance personnel use to withhold resuscitation from these individuals?

While the conclusion that the addition of other skills (drug administration and intubation) might save "a few extra lives" is probably correct, we are concerned that this study together with the results of the Scottish experience of semiautomatic defibrillators[1] may stop full extended training in ambulance aid being given to paramedics.

We have already shown the effectiveness of personnel with extended training in the management of hypoglycaemic coma.[2] There is recent evidence that patients with acute myocardial infarction complicated by hypotension and bradycardia have a better outcome when transported to hospital by a paramedic vehicle rather than an ordinary ambulance.[3] Personnel with extended training also treat patients with acute asthma,[4] hypovolaemic shock, and respiratory arrest, and in the future may administer thrombolytic agents.[5]

We are sure that the provision of a defibrillator on every emergency ambulance is an essential short term aim for improving the prehospital management of cardiac arrest. We are equally certain that the provision of a paramedic on every vehicle, coupled with a strict clinical audit, is the essential long term approach to improving *all* aspects of prehospital emergency care.

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1 Cobbe SM, Redmond MJ, Hollingworth J, Carrington DJ. Heartstart Scotland: initial experience of a nationwide scheme for out of hospital defibrillation by ambulance crews [Abstract]. *Br Heart J* 1990,64:65.
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BOOK REVIEW

Practical Echocardiography in the Adult. J P M Hamer. (Pp 229; £79.50.) Dordrecht, The Netherlands: Kluwer Academic Publishers, 1990. ISBN 0792306708.

There are many large detailed reference texts for those experienced in echocardiography and Doppler. However, there is a dearth of books, like this one, giving practical advice and tips to those starting and learning the technique.

The book is approximately 200 pages long and liberally illustrated with high quality diagrams and echocardiographic/Doppler images. Unfortunately, many of the images and Doppler recordings have been reproduced in a rather small format and this does not do them justice. Dr Hamer has attempted to cover every aspect of adult echocardiography and with each cardiac structure he has described what features the echocardiographer should examine and what measurements to make. This is indeed good practical advice and to my knowledge is not presented in this form elsewhere.

In discussing each abnormality Dr Hamer has very sensibly integrated the role of all the echocardiography and Doppler techniques including transoesophageal echocardiography. There is also a small but excellent chapter on reporting echocardiograms which I believe would be of particular value to nonclinicians.

There is undoubtedly a need for practical books on echocardiography and I am sure that this volume will prove popular. However, while the range of topics covered is very comprehensive this has unfortunately caused a lack of detail and omission of many practical pointers which those new to the technique would have undoubtedly found useful.

MARK J MONAGHAN

BRITISH CARDIAC SOCIETY NEWSLETTER

The office move was completed uneventfully, and we now have more space. At present the society occupies three rooms at the top of numbers 1 and 2 St Andrew's Place, and we hope to have the fourth room shortly. We can now accommodate committee meetings, and once we have a large enough table (we hope second hand) full council meetings should also be possible in our own premises. Please note that our address is Number 1. We have given up one telephone number but now two lines are available on 071-486 6430.

The Glasgow meeting is approaching. We have made one more break with tradition in that we are liaising with our public relations consultants to encourage the presence of the media. Our constitution states that the press will not be admitted to scientific sessions, and this will be upheld. But we plan to offer briefing sessions where we will be prepared to discuss items of interest that are expected to be presented that day, and to comment on items that may have been presented on the previous day. This will of course be conditional on agreement with the authors. We hope that the senior author or a nominee will agree to be present if we know that a particular paper is likely to attract interest. The health and medical correspondents of the London daily newspapers may not wish to travel to Glasgow. If necessary we may be able to arrange a meeting in London beforehand with an embargo on any premature publication. Particular care must be taken not to encourage or indeed permit detailed publication in the lay press of scientific data that should first appear in medical journals. We believe that there may be enough interest in general discussion of topics that are of legitimate public interest. This is being tried as an experiment, and experience will show whether or not there is good reason to repeat it. Another initiative we plan with the media will involve occasional lunch time meetings with one or two correspondents. Their principal purpose is to establish contact which will aid liaison in the future rather than to seek publicity over current issues.

We consulted the Royal College of Physicians over the title for the new post of specialist career advisor. The suggestion of Postgraduate Dean might, it was felt, cause confusion with Regional Postgraduate Deans. We have therefore accepted advice that Howard Swanton should be known as Postgraduate Cardiology Advisor. We hope that members of the society or indeed others seeking a future in cardiology will consider consulting him if they need specialist information that can supplement the help they will receive from Regional Postgraduate Deans: we do not seek to duplicate a service that is already available and of proven value.

Members of the society should now be aware of the need to register completion of specialist training in cardiology with the General Medical Council, although the entry will show only T(M) for general medicine. Many currently in consultant posts did not have the opportunity to become accredited because the scheme did not exist during their training years. For an interim period all who have been appointed to a consultant post with the agreement of a representative of one of the medical Royal Colleges can obtain registration. This clause should embrace all who hold National Health Service contracts at consultant level. Those wishing to take advantage of the "grandfather clause" (the name was invented by one more considerably distinguished than ourselves) should write to the registrar of the college and should receive in return a copy of a formal letter to the General Medical Council. We suggest you take this action without delay.

A meeting was held at the Royal College of Physicians in February for National Health Service managers entitled "New Approaches in Cardiology". The programme was arranged by Michael Petch. The topic of heart transplants led to a lively discussion, especially on cost implications. Other presentations dealt with thrombolysis, angioplasty, electrical treatments, training, and academic cardiology This was a useful meeting. We do not do as much as we should to give our administrators the background information they need. The increase in the cost of pacemakers (modest we hope) that will almost certainly occur because of the closer financial ties with Europe from 1992 was news to many. A show of hands indicated that few had been warned of this by their local cardiologists. That seemed a good indication of a failure of communication that is worth pondering. Perhaps some cardiologists are not aware that harmonisation (which is the appropriate jargon word) will bring some financial penalties?

Two health authorities have been told by the National Health Service Executive that they may not readvertise senior registrar posts when they fall vacant. Three posts are involved. This has been brought to our attention only in the last week or so, though one letter was received in December. There was a clear implication that these particular changes, needed in order to meet imposed quotas, were agreed at a JPAC review in consultation with the specialty. This is not so. The Royal College of Physicians, the Specialist Advisory Committee, and the British Cardiac Society were all unaware of the action that had been taken. Our numbers are approximately correct by the formula of the Joint Planning Advisory Committee, but may not take account of the arbitrary 20% "top slice" removed from our allocation for the research pool (which is not specialty specific). We have disputed the need and the logic of this curious system that may underlie these recent cuts. We believe that any action to cancel a senior registrar post should be the subject of negotiation with the specialty, and we hope that the National Health Service Management Executive will have second thoughts about the wisdom of actions taken without appropriate consultation. "Achieving a Balance" can be made to work effectively only if a spirit of cooperation is maintained. We have striven to play our part. If any readers know of further actions of this type we would like to know without delay.

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NOTICES

1991

The Annual Meeting of the **British Cardiac Society** will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May. The closing date for receipt of abstracts was 10 December 1990.

XVIII Argentine Congress of Cardiology will be held in Buenos Aires on 18 to 21 September: Sociedad Argentina de Cardiologia, Azcuénaga 980, 1115 Buenos Aires, Argentina (Fax: +54-1-961 6020; Tel: +54-1-961-6027/29).

12th international symposium on **Computer Assisted Decision Support and Database Management in Anaesthesia, Intensive Care and Cardiopulmonary Medicine** will be held in Rotterdam on 2 to 4 October: Dr Omar Prakash, Thorax Anaesthesia, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands (Fax. 31-10-463 5240; Tel: 31-10-463 5230).

1991 Pfizer international research symposium on **Epidemiology of Peripheral Vascular Disease** will be held in Edinburgh on 31 October and 1 November: Clare Perry, Edinburgh Post-Graduate Board for Medicine, Pfizer Foundation, 11 Hill Square, Edinburgh EH8 9DN (Tel. 031 650 2610).

Br Heart J 1991;65:237–8

BRITISH
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Editorial

Is cardiac rehabilitation necessary?

Eight to 38% of patients do not return to work after myocardial infarction though many of them seem physically capable of resuming employment.[1] The cost of myocardial infarction is high and is mainly the result of vocational disability. In the 1970s and 1980s many studies were designed to test the premise that rehabilitation after infarction improves the patient's psychological state and exercise capacity and reduces mortality. Cardiac rehabilitation is defined as a process by which patients with cardiac disease are restored to their optimal physical, medical, psychological, social, emotional, vocational, and economic status.[2]

Exercise capacity

Exercise capacity after myocardial infarction is impaired by the reduced response of cardiac output to exercise and the deconditioning effect of bed rest and physical inactivity. Some randomised and controlled studies have examined whether rehabilitation improves physical work capacity more than would be expected to occur spontaneously.[3–7] The contradictory results probably relate to differences in exercise training programmes, the role of non-exercise treatment such as counselling, time of enrolment after infarction, and differences in the patient populations studied. Overall analysis of available data suggests that supervised physical exercise can be expected to increase a patient's maximal exercise capacity after infarction by an average of 15–25% over that which would occur spontaneously.[8]

Many, predominantly sedentary patients, without complications whose recreational and occupational activities are of low intensity resume their former activities without participating in a formal cardiac rehabilitation progamme. It is unclear, however, which patients are most likely to benefit. Hammond *et al* reported that the best predictor of improvement in exercise performance at one year was a low initial exercise capacity.[9] But their results did not accord with those of Van Dixhoorn *et al*[10]—perhaps because in the latter study[10] exercise capacity was not expressed as a percentage that predicted for age. A small improvement in exercise capacity might enable people with a poor exercise capacity after myocardial infarction to return to a reasonable level of activity. Cardiac rehabilitation may also benefit those with an initially good exercise capacity, though the improvement will be of less clinical importance.

The study by Goble *et al* reported in the March issue of the *British Heart Journal* showed that the physical benefits of aerobic exercise training can be as easily achieved with light exercise as with heavy exercise.[11] The mechanism of the improvement in exercise capacity after cardiac rehabilitation is not clear. There is no totally objective method of assessing exercise capacity and hence increased patient motivation may result in an apparent improvement in physical state. Goble *et al*'s study found that only 41% of patients who enrolled in the light exercise programme attended more than three quarters of their classes. Is the "improvement" in exercise capacity with both exercise regimes related to the type of exercise protocol or to reassurance of the patient by close, regular contact with a paramedical worker or doctor?

Most cardiac rehabilitation programmes have not evaluated the effects on patients with cardiac failure. Contrary to previously held belief, patients with severe left ventricular dysfunction who participated in an organised rehabilitation programme improved their exercise capacity.[12 13] But those who have suffered a large anterior myocardial infarction (who might eventually develop overt heart failure) may deteriorate if enrolled in a rehabilitation programme soon after infarction.[14]

Psychosocial function

As expected, the results of the studies of the effects of cardiac rehabilitation and psychosocial function have been inconsistent. Psychosocial data are difficult to quantify. Reports in uncontrolled studies frequently describe a substantial improvement in psychological wellbeing related to cardiac exercise programmes. Data from the few randomised control studies suggest less impressive effects of exercise on psychological wellbeing and question whether the improvement documented relates to close review of the patient rather than participation in a formal exercise programme.[15–18]

No significant improvement was reported in occupational state in well designed assessments of cardiac rehabilitation. The conclusion of an extensive review on the subject was that special programmes of cardiac education, teaching, or psychological support and counselling over and above usual supportive care should not be recommended as routine measures after myocardial infarction.[8] This is not to say, however, that selected patients might not require special teaching and counselling in addition to routine care because of psychological distress or a lack of knowledge.

Mortality

Once again, difficulties in study design have precluded definitive conclusions on mortality. Unfortunately, most studies have predominantly focused interventional effort on low risk patients. Consequently, because of a type II statistical error, studies of small groups of patients might "erroneously" conclude that rehabilitation fails to reduce mortality. Only one of the major randomised trials of exercise in cardiac rehabilitation after infarction reported a significant reduction in cardiac mortality.[19] There were slightly more than 700 in the largest study.[20]

This issue was reviewed by meta-analyses three times in the 1980s. May *et al* reviewed various interventions after myocardial infarction and reported a significant 19% decrease in cardiovascular mortality with an exercise programme.[21] Oldridge *et al* and O'Connor *et al* combined the randomised exercise trials of the 1970s and 1980s (including over 2000 patients).[22 23] Significantly lower pooled odds ratios—0·75 and 0·78 respectively—were reported. However, pooling of data in these studies might be inappropriate. There were differences in patient populations, mortality, and exercise programmes between studies. Given the presumed pathogenetic mechanisms involved in altering the atherosclerotic process it is unlikely that relatively short term programmes of exercise, for example less than four or five years, would substantially alter mortality and morbidity in patients with coronary artery disease. Perhaps a longer habitual increase in physical activity after infarction could reduce morbidity and mortality, as has been shown in certain long term studies of healthy people or in men originally at high risk from coronary disease as predicted by high concentrations of cholesterol, high blood pressure, or cigarette smoking. Such an assertion, however, currently cannot be supported by the existing data and must remain hypothetical.

Risk factor modification

When Kallio *et al* used a multifactorial intervention they found substantial changes in risk factors in their special intervention group.[19] Other studies (not multifactorial but typically exercise only) showed less impressive or no changes in risk factors. On the basis of these studies an exercise programme alone seems unlikely to produce better risk factor outcomes when applied to unselected patients after myocardial infarction.

Conclusions

The analysis of the effects of cardiac rehabilitation is hampered by the heterogeneity of the patients studied. Formal exercise programmes are probably not justified for all patients. Certain patient subgroups may benefit, for example those with a low exercise capacity or chronic exercise limitation caused by severely depressed left ventricular function. The major beneficial effect of rehabilitation programmes may be associated with the reassurance provided by close contact with paramedical staff. Further trials are required to evaluate which components of the rehabilitation programme benefit the individual patient.

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Br Heart J 1991;65:239–44

ORIGINAL ARTICLES

Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients

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Abstract

Heart rate variability was measured in 77 healthy controls and 343 diabetic patients by a count of the number of beat-to-beat differences greater than 50 ms in the RR interval during a 24 hour ambulatory electrocardiogram. In the healthy controls the lower 95% tolerance limits for total 24 hour RR interval counts were approximately 2000 at age 25, 1000 at 45, and 500 at 65 years. Six controls confined to bed after injury had normal 24 hour patterns of RR counts, while eight other controls showed loss of diurnal variation in both heart rate and RR counts during a period of sleep deprivation. RR counts in ten controls on and off night duty increased during sleep whenever it occurred. Nearly half (146) the 343 diabetic patients had abnormal 24 hour RR counts. The percentage of abnormal RR counts increased with increasing autonomic abnormality assessed by a standard battery of tests of cardiovascular autonomic function. A quarter of those with normal cardiovascular reflex tests had abnormal 24 hour RR counts. There were close correlations between 24 hour RR count results and the individual heart rate tests (r = 0·6).

The assessment of cardiac parasympathetic activity by 24 hour RR counts was reliable. The diurnal variations in RR counts seen in the controls were probably related to sleep rather than either posture or time of day. The method was more sensitive than conventional tests of cardiovascular reflexes.

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Measurements of heart rate variability are increasingly being used as markers of cardiac autonomic activity. In diabetes and other clinical disorders affecting the autonomic nervous system their use is now well established.[1] The variability in heart rate may be an independent prognostic marker after myocardial infarction,[2] and an imbalance of normal cardiac autonomic control mechanisms, with reduced heart rate variation, has been proposed to explain sudden infant death syndrome.[3] Diurnal variation in the pulse rate was noted in a medical journal as long ago as 1815,[4] but the use of short term heart rate variation as a clinical test of autonomic function both at rest[5] and during a short period of deep breathing[6] was only developed in the 1970s. More recently still, heart rate variation has been measured over longer periods by 24 hour electrocardiographic tape recordings.[7] As a diagnostic clinical test, the maximum − minimum heart rate during deep breathing has proved most popular[6,8,9] but for research purposes other methods of analysis, including the use of standard deviation[2,5] and spectral analysis,[10–12] have also been used.

Though these approaches are valid they also have drawbacks. For example, the "deep breathing" method has relatively poor reproducibility, is dependent on the subject's cooperation, and only gives information about the brief period during which the heart rate is actually measured. Scrutiny of longer heart rate recordings often shows considerable discrepancies in the amount of heart rate variability present at different times of the day and night (fig 1). Spectral analysis is based on assumptions about the control of heart rate which depend on particular and consistent input stimuli and on the assumption that its rhythms can be broken down into discrete components, each representing specific and different autonomic activity. Spectral techniques are also unable to cope with recordings containing frequent ventricular arrhythmias. Standard deviation methods do not distinguish clearly between parasympathetic and sympathetic components.

Because of the limitations of these methods, we have developed an alternative approach. We noted that there were a large number of beat-to-beat changes in heart rate that occurred frequently but irregularly in healthy controls and that they were distinct from the smaller cyclical changes of respiratory sinus arrhythmia. We devised a method to measure these larger changes by counting the number of times successive RR intervals differed by more than 50 ms during a 24 hour tape recording (referred to subsequently as "RR counts"). This was first described in 1984 when we showed that RR counts reflected the integrity of cardiac parasympathetic pathways.[7]

The aim of our present study was to determine what factors affect heart rate variability— in particular the role of posture, sleep, and time of day. We evaluated the results from our

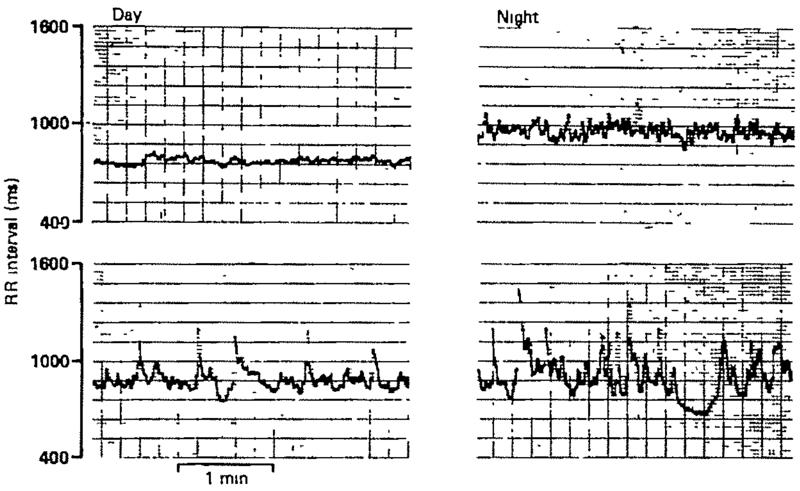

Figure 1 Four short RR interval recordings (3 minutes each) taken from the same diabetic patient at different times of the day and night, showing considerable differences in RR variation.

larger experience of 24 hour electrocardiographic tape analysis and defined the age related normal values for the RR counts. We also sought to establish how the results of 24 hour electrocardiographic tape recordings relate to conventional tests of cardiovascular autonomic function in a large group of diabetic patients.

Patients and methods

CONTROLS

Twenty four hour electrocardiograms were recorded from 57 men (aged 18–65 years) and 20 women (aged 18–57 years). All were ambulant and going about their normal daily routines. None had any known disease or was taking regular medications (normal group). Tapes were also recorded from six young men (18–27 years) who were confined to bed with leg and pelvic fractures. The tapes were recorded several days after operation when the men were fully conscious (orthopaedic group). Eight other healthy young men (aged 19–29 years) took part in a sleep deprivation study, during which heart rate was monitored on to tape for 24 hours before, for two successive 24 hour periods during 48 hours continuous sleep deprivation, and then on two successive 24 hour recovery periods of normal sleep (sleep deprived group). The results from the two 24 hour tapes measured during sleep deprivation were averaged as were those from the 48 hours recovery period. Ten night nurses (three men and seven women, aged 26–47 years) had 24 hour tape recordings made during and after their night duty shifts (night shift group). Four recordings were made on each individual: at the beginning and end of seven days of night duty and at the beginning and end of their seven day recovery period off duty. The 24 hour RR counts in men in the normal group and the "posture" results in the orthopaedic group have been described briefly before[13] but are included here in greater detail.

DIABETIC PATIENTS

Three hundred and twelve diabetic patients (200 men and 112 women, aged 17–66 years) had 24 hour recordings as part of their assessment for autonomic involvement (diabetic group). Twenty four hour tape recordings and a standard battery of cardiovascular reflex tests were performed within 24 hours of each other in all these patients. A further 31 diabetic patients had an incomplete battery of cardiovascular tests. Their results are included in the correlations between the 24 hour tape results and individual tests.

The subjects in the various studies all agreed to 24 hour ambulatory electrocardiographic monitoring and the technique had the approval of the local hospital ethics advisory committee.

METHODS

Electrocardiographic recordings

Three chest electrodes were used to record electrocardiogram signals on to a cassette tape with an ambulatory electrocardiographic monitoring system (Medilog, Oxford Instruments or Tracker, Reynolds Medical). An adjacent tape track was used to record a simultaneous time frequency reference signal. The recordings were continued for 24 hours, while the subjects went about their routine daily activities, with the tape recorder carried on a belt worn around the waist. They noted meal times, unusual events, and the times of going to bed and getting up in a diary.

Analysis of RR interval variation

The 24 hour tapes were later replayed through a Pathfinder (Reynolds Medical) high speed arrhythmia analyser at 120 times the original recording speed. The replay speed was controlled to within 0·5% by means of the time reference track recorded on each tape.

The trigger section of the analyser detected individual QRS waves in the electrocardiogram signal and distinguished them from P and T waves and from muscle noise and artefact by means of a continuously adaptive threshold derived from the noise components by independent filtering. The accuracy with which QRS waves can be detected depends on the quality of the recorded electrocardiogram; with tapes of routine quality there were only about 12 false positive and false negative errors of detection in 24 hours.[14] Excessive noise, such as would cause QRS waves to be missed, automatically inhibited analysis until the noise subsided, whereupon analysis was resumed. The Pathfinder detects any QRS waves with a shape that differs significantly from the subject's "normal" QRS complex; a continuously updated example of this normal complex is held in the analyser memory for comparison. Such abnormal complexes are indicated as ventricular extrasystoles.[15] The signal is closely monitored throughout the analysis by the operator to exclude tapes with atrial fibrillation and other non-sinus rhythms, and appreciable numbers of supraventricular extrasystoles.

For each electrocardiographic complex in the recording the Pathfinder generates an external pulse to signify a beat, and another if that QRS complex is of normal (sinus) configuration. These pulses are passed to a microcomputer which times the arrival of each beat and calculates the length of each RR interval and the difference between each successive beat. If this increases by more than 50 ms between successive beats a positive count is added to the total being accumulated. Likewise, if the change shows a decrease of more than 50 ms the total negative count is increased. Because we found no significant differences between positive and negative counts[7] the results reported here are positive counts.

The program also continuously maintained time thresholds corresponding to 63% and 175% of the prevailing normal RR interval. Beats with intervals outside these limits together with all those indicated by the Pathfinder as being "not normal" in shape were rejected and the interval calculations were restarted from the next normal QRS. The intervals thus excluded and all periods during which the analyser was inhibited were accumulated and used to calculate the percentage of the time actually analysed. Using this technique we can now analyse tapes with large numbers of ventricular extrasystoles.[16] For each tape the program gave an output of total 24 hour RR counts, mean hourly wake and mean hourly sleep RR counts, and mean wake and mean sleep heart rate. Where the tape recording is incomplete the results are normalised to the equivalent of 24 hours. Recordings shorter than 18 hours or with less than 40% of beats analysed were rejected.

Cardiovascular autonomic function tests

We used a standard battery of cardiovascular autonomic function tests to assess all diabetic patients: the heart rate responses to the Valsalva manoeuvre, standing up, and deep breathing; and the blood pressure responses to standing up and sustained handgrip. We have described these tests and the grading of severity in detail elsewhere.[9] In brief, autonomic involvement was categorised as normal (all tests normal), early (one heart rate test abnormal), definite (two or more heart rate tests abnormal), severe (abnormal heart rate tests plus one or both blood pressure tests abnormal), or atypical (any other combination of abnormalities). Autonomic scores were derived by giving each test a score of 0 for normal, 1 for borderline, and 2 for an abnormal result. This gave a total score of between 0 (normal) and 10 (most severe).

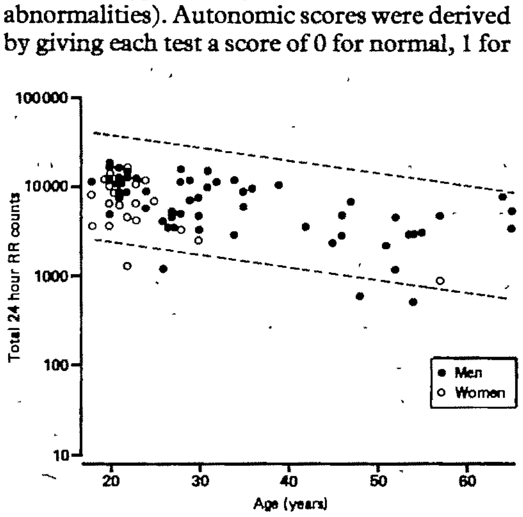

Figure 2 Individual total 24 hour RR counts in 57 healthy men and 20 healthy women. The broken lines are the age related 95% normal tolerance limits, derived from the counts in the 57 men.

STATISTICAL ANALYSIS

Conventional statistical methods were applied to the results as appropriate; we used regression calculations and paired *t* tests. Where the data were not normally distributed calculations were performed on the log transformed data. Results are accordingly presented as mean (SD) or geometric mean and range.

Results

CONTROLS

There were significant inverse correlations between age and total 24 hour ($r = -0{\cdot}55$), mean hourly wake ($r = -0{\cdot}54$), and mean hourly sleep ($r = -0{\cdot}51$) RR counts in the 57 male controls. Figure 2 shows the individual total 24 hour RR counts in these men and in 20 female controls. Because there were no significant differences between the results of the men and women and because the age distribution of the women was skewed (most were < 30 years old), the lower 95% tolerance limits for the RR counts were calculated from the results for the 57 men. The normal lower 95% tolerance limits for total 24 hour RR counts are 2000 at age 25, 1000 at age 45, and 500 at age 65 years. Table 1 shows the equivalent values for mean hourly wake and sleep RR counts.

ORTHOPAEDIC GROUP

All six young men confined to bed after injury had total 24 hour RR counts well within the normal range for their age (fig 3). The counts rose appropriately at night during sleep in five subjects (geometric mean of hourly wake counts 235 (84–792) and hourly sleep counts 484 (249–716)). All wake and sleep values were in the normal range. Mean heart rate fell from 77 (7) beats/min awake to 61 (6) beats/min asleep.

SLEEP DEPRIVED GROUP

Table 2 shows the group mean RR counts and heart rate during normal sleep and during sleep deprivation. There were no significant differences in results between the normal 24 hour period before and the 48 hour period after sleep deprivation. Mean RR counts rose as expected during normal sleep from 452 to 614 (+36%, $p = 0{\cdot}034$), but not at night during sleep deprivation (460 to 471) (+2%, NS). Heart rate fell substantially during normal sleep, but during sleep deprivation day and night values remained similar. There were, therefore, considerable differences between the night time

Table 1 Approximate normal lower 95% tolerance limits for total 24 hour, mean hourly wake, and mean hourly sleep RR counts related to age

Age (yr)	*Total 24 hour counts*	*Mean hourly wake counts*	*Mean hourly sleep counts*
25	2000	60	90
45	1000	30	45
65	500	15	20

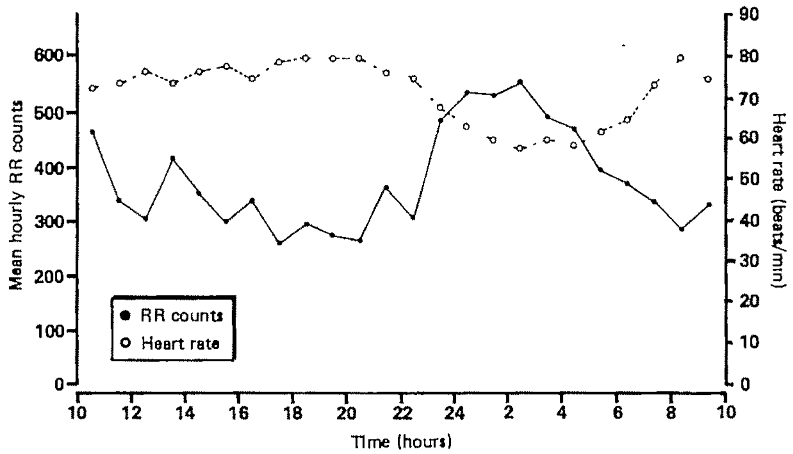

Figure 3 Group mean hourly RR counts and hourly heart rate in six young men confined to bed.

counts (p = 0·059) and heart rates (p < 0·001) during the normal and the sleep deprived periods.

NIGHT SHIFT GROUP

During the first and last night shift periods, which were separated by six days, the wake/sleep pattern was similar, with an average of seven hours sleep on each occasion, taken between about 9.00 am and 5.00 pm. On coming off night duty, the subjects usually slept during the day until about 5.00 pm, then got up, and went back to bed again around 12.00 midnight until 7.00 or 8.00 am the following morning. This meant that during the first day they had an average of 13 hours' sleep. Six days later, the last day shift, the sleep pattern had reverted to normal, but in preparation for their next night duty shift, the subjects slept longer—an average of 10 hours from midnight to 10.00 am.

The hourly RR counts during these four 24 hour periods reflect the wake and sleep patterns (fig 4) in that during the two night shift periods the average RR counts were highest during the day when the subjects were asleep (geometric mean of hourly counts: wake 123 (13–585) and 140 (35–462); sleep 188 (47–1167) and 234 (32–835)). The last day shift period, just before the subjects restarted night duty, shows a normal day/night pattern of RR counts (wake 174 (29–541); sleep 331 (96–1021)). The first day shift period, however, shows a somewhat different pattern, with two periods of higher and two periods of lower counts, corresponding to the two periods of sleep and waking. This was coupled with higher and lower mean heart rates (geometric mean of hourly counts—wake first period 144 (34–673), wake second period 154 (46–640); sleep first period 255 (74–857), sleep second period 344 (82–940) and mean heart rates (beats/min)—wake 78 (10) and 78 (8); sleep 66 (8) and 62 (5) sleep). Because the counts were higher during sleep, the mean total 24 hour RR counts were greatest during the day shift periods when the subjects slept more (first night shift 3583 (582–18119), last night shift 4168 (811–13514), first day shift 6425 (2182–17644), last day shift 5905 (1922–16191)).

DIABETIC GROUP

Forty seven per cent (146 subjects) had total 24 hour RR count results that were less than the lower 95% tolerance limit for healthy controls related to age. Table 3 shows the proportion of normal and abnormal results related both to the autonomic category and to the autonomic score (based on results from a standardised battery of cardiovascular reflex tests done within 24 hours of the 24 hour tape recording). With increasing autonomic abnormality there was a higher percentage of abnormal 24 hour tape results; so that almost all with autonomic dysfunction in the "definite" and "severe" categories had abnormal total 24 hour counts. The fact that the 24 hour tape method is more sensitive than conventional autonomic function tests is shown by the 24% who had abnormal 24 hour counts despite normal cardiovascular reflexes. Table 3 also shows the group mean values for the 24 hour count results related to autonomic category and score. Counts were lower as the autonomic damage increased.

Table 4 shows the correlation coefficients between the 24 hour total counts, wake and sleep counts, and the individual cardiovascular autonomic function tests. In every case the relations were highly significant statistically, with the closest correlation between the counts and the heart rate tests. There were also extremely close correlations between the log total 24 hour counts and the log wake counts (r = 0·969) and the log sleep counts (r = 0·957) in this group of diabetic patients.

Discussion

Since we first reported our technique of assessing cardiac parasympathetic activity by

Table 2 Group mean RR counts and heart rates in eight healthy men aged 19–29 years who were deprived of sleep for 48 hours

	RR counts (geometric mean and range)			*Heart rate (arithmetic mean (SD)) (beats/min)*	
	Total 24 h counts	*Mean hourly wake*	*Mean hourly sleep*	*Wake*	*Sleep*
		p = 0·034			
Normal sleep	12333 (7332–18050)	452 (300–737)	614 (263–877)	79 (8)	57 (8)
Significance	NS	NS Day (8 am–12 pm)	p = 0·059 Night (12 pm–8 am)	NS Day	p < 0·001 Night
Sleep deprived	11194 (5951–17723)	460 (217–761)	471 (310–754)	77 (8)	76 (8)
		NS			

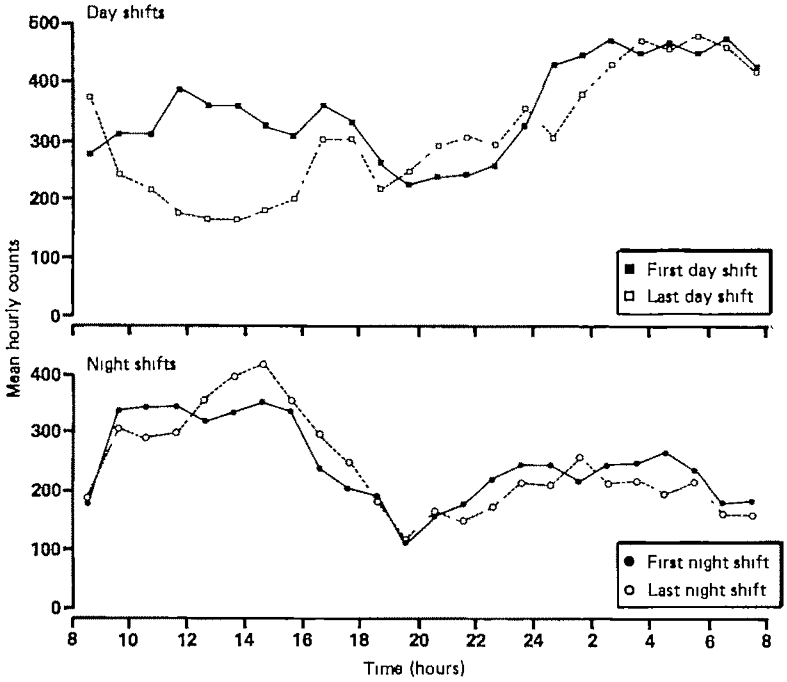

Figure 4 Group mean hourly RR counts in ten healthy individuals (three men and seven women) during and after night duty.

analysing 24 hour electrocardiograms,[7] we have gained considerably more experience in both healthy individuals and patients. The method has also been refined so that we can now exclude large numbers of ventricular extrasystoles without losing the essential data on heart rate variability.[16] This contrasts with the inability of spectral analysis methods to handle ventricular extrasystoles. Additionally, analysis can be done at 120 times real speed so that a full 24 hour tape recording can be read through in twelve minutes by the dedicated microcomputer system we have developed.

In a smaller study we showed that RR counts decrease with age in healthy individuals. We have expanded our normal results and in the present study we show the 95% tolerance limits not only for the total 24 hour RR counts but also for the mean hourly wake and mean hourly sleep counts. There was an extremely close correlation between these three measures in the results from the diabetic patients, which means that each index can be used to assess variability. We previously reported our data on repeatability in healthy individuals, diabetic patients, and patients with cardiac disorders,[7 16] showing that this RR counts method can be used reliably for treatment and outcome trials.

There is normally a characteristic rise in RR counts at night and we wondered what factors might be responsible for this. We found a normal RR counts pattern in a group of fit but immobile young men. This suggests that being confined to bed is not a factor influencing the numbers of abnormal RR counts recorded.

To establish whether the variations in RR counts were part of a built-in diurnal clock we measured RR counts in another group of fit young men undergoing prolonged periods of sleep deprivation as part of a different study. Though total 24 hour RR counts were similar, the wake/sleep difference in counts during the period of "normal sleep" disappeared during the 48 hours of sleep deprivation. Similarly, in a group of nurses the daytime counts were higher while the nurses were on night shift and sleeping during the day. There is, therefore, no built-in diurnal clock to regulate the RR counts.

The third candidate for modifying RR counts is that of sleep itself, rather than either posture or time of day. The results from both the sleep deprivation and the night duty studies support this mechanism: both periods of sleep taken by the night duty staff on the same day increased the RR counts. Thus the increase in RR counts seen in most individuals occurs during sleep and seems to be due to sleep itself. This would fit in with current concepts of the relative activity of the autonomic nervous system whereby both sympathetic and parasympathetic components are active during the day, whereas at night during periods of non-rapid eye movement sleep there is predominantly parasympathetic activity. This is also reflected in the changes in heart rate which reciprocate the changes in RR counts in most individuals. We have not specifically related sleep stages to RR counts but during rapid eye movement sleep there are well documented changes in autonomic activity[17] which may be associated with increased RR counts.

Do RR counts merely reflect the overall heart rate? We argued in detail that this is not so[7 13] in view of the dissociation between heart rate and heart rate variability in our earlier studies.[16] There is a complex interrelation between beat-

Table 3 Number of diabetic patients with abnormal 24 hour RR counts according to autonomic category and score, and group mean values for RR counts

	Number with 24 hour RR counts		*Group mean 24 hour RR counts (geometric mean)*		
	Total	*Number with abnormal counts (%)*	*Total 24 hour*	*Mean hourly wake*	*Mean hourly sleep*
All	312	146 (47)			
By autonomic category					
Normal	147	35 (24)	2845	84	170
Early	52	25 (48)	866	27	42
Definite	32	27 (84)	154	6	7
Severe	60	51 (85)	114	4	4
Atypical	21	8 (38)	1489	48	69
By autonomic score					
0–2	175	42 (24)	2756	82	162
3–5	67	43 (64)	422	14	19
6–10	70	61 (87)	112	4	4

Table 4 Correlation coefficients between individual cardiovascular autonomic function tests and total 24 hour RR counts and mean hourly wake and sleep RR counts

RR counts	*Valsalva ratio*	*30.15 ratio*	*Max − min heart rate*	*BP drop on standing*	*BP rise with grip*	*Autonomic score*
Log total 24 hour	0·627 (n = 321)	0·557 (n = 342)	0·625 (n = 285)	−0·439 (n = 316)	0·314 (n = 312)	−0·683
Log mean hourly wake	0·636 (n = 318)	0·567 (n = 340)	0·637 (n = 286)	−0·433 (n = 313)	0·297 (n = 311)	−0·679 (n = 309)
Log mean hourly sleep	0·610 (n = 318)	0·539 (n = 340)	0·608 (n = 286)	−0·444 (n = 313)	0·323 (n = 311)	−0·692 (n = 309)

to-beat differences and prevailing average heart rate, but it is by no means a simple matter of the overall heart rate determining the amount of beat-to-beat heart rate variation, however measured.

Though we showed the clear relation between autonomic damage and RR counts in our original article[7] and briefly in a small group of diabetic patients[19] we have not hitherto reported in detail on the relation between conventional non-invasive tests of cardiovascular autonomic function and 24 hour RR counts in large numbers of diabetic patients. Our results clearly show not only the very close correlations achieved between individual cardiovascular tests (particularly the heart rate tests) and RR counts, but also the differing proportions of normal and abnormal results with increasing severity of autonomic damage. About 85% of those in whom definite or severe damage was detected by cardiovascular testing had abnormal RR counts. Because 24% of diabetic patients with apparently normal cardiovascular reflexes had abnormal RR counts we believe that the RR counts method is more sensitive than conventional tests of cardiovascular reflexes.

What are the clinical applications of this method? It is reliable and sensitive and gives an objective measure of cardiac parasympathetic activity.[7] Simple bedside tests of autonomic function in diabetes are widely available to diagnose autonomic neuropathy,[1 9] but our method of analysing 24 hour electrocardiographic tape recordings reveals earlier abnormalities of cardiac parasympathetic function. There has recently been increasing interest in the effect of autonomic influences on prognosis after myocardial infarction. With our method it should be possible to see whether low heart rate variability is indeed an adverse prognostic indicator. One such study has already been published,[2] and further studies are currently in progress by our own group and others. Conventional bedside tests are also inappropriate in the sudden infant death syndrome, where there has been evidence that reduced heart rate variation may be a factor.[3 20] Objective assessment of other conditions such as chronic renal failure, liver disease, and congestive cardiac failure may also be possible with this method of 24 hour electrocardiographic tape recording. Other work in progress suggests that measurement of RR counts may also be of relevance in assessing the effect of drugs on the cardiovascular system.[16 21]

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Oxygen free radicals and congestive heart failure

J J F Belch, A B Bridges, N Scott, M Chopra

Abstract

Plasma lipid peroxides (malondialdehyde) and thiols were measured in 45 patients with congestive heart failure and 45 controls. Malondialdehyde concentrations were significantly higher in the patients with congestive heart failure (median 9·0 nmol/ml interquartile range (IQR) 7·9–10·2) than in the controls (median 7·7 nmol/ml (IQR 6·9–9·2)). Plasma thiols were significantly lower in congestive heart failure (median 420 μmol/l (IQR 379–480)) than in the controls (median 463 μmol/l (IQR 445–525)). There was a significant but weak negative correlation between malondialdehyde and left ventricular ejection fraction (r = − 0·35) and a positive correlation between plasma thiols and left ventricular ejection fraction (r = 0·39).

This study provides clinical support for experimental data indicating that free radicals may be important in heart failure. It also suggests that the degree of free radical production may be linked to the severity of the disease.

In congestive heart failure the heart is unable to provide sufficient blood for tissue metabolic needs. Congestive heart failure affects about 1% of the population[1] and carries a poor prognosis with an annual mortality of between 35% and 58%.[2] The pathophysiology of this disorder is undoubtedly multifactorial but the cellular mechanisms at the molecular level have not been fully elucidated.

Oxygen free radicals have been implicated in cardiac ischaemic injury.[3 4] These free radicals (superoxide anions and hydroxyl radicals) are produced in the body by reduction of oxygen. In normal circumstances they are removed by the different scavenger systems present in blood and tissue. We believe that free radicals are involved in the genesis of heart failure. In congestive heart failure myocardial contractility is impaired by loss of muscle or by pressure or volume overload.[5] This pressure and volume overload causes myocardial ischaemia which can generate free radicals.[3 4] Support for this hypothesis comes from work in animal models of heart failure where doxorubicin toxicity may result from myocardial injury induced by oxidative damage.[6] Furthermore, it has been shown that polymorphonuclear leucocytes from dogs with congestive heart failure produce increased amounts of free radicals.[7] In humans congestive heart failure is associated with an increase in production of prostaglandins. The formation of prostaglandins is associated with the production of oxygen derived free radicals through the arachidonic acid pathway.[8] Furthermore, circulating catecholamine production increases in the failing heart and their auto-oxidation generates free radicals.[9] There is therefore some evidence to suggest an involvement of free radicals in congestive heart failure.

We measured the products of free radical reactions in patients with congestive heart failure. The inherent reactivity of radical species with organic biomolecules precludes their direct measurement in biological systems. Their presence has to be inferred from their known effects, such as the induction of protein fluorescence and oxidation of polyunsaturated fatty acids. Two such systems, the measurement of lipid peroxides by the thiobarbituric acid test[10] and the measure of plasma thiols,[11] have been carried out here and correlated with the left ventricular ejection fraction—a measure of the severity of congestive heart failure.

Patients and methods

We studied 45 patients aged under 75 with congestive heart failure diagnosed by a team of hospital physicians. Most patients were thought to have atherosclerosis as the underlying cause of their congestive heart failure. All patients gave informed consent for the study and the study was approved by the hospital ethics committee. Patients with other disorders or receiving medication known to affect free radical activity were excluded from the study. No adjustment was made to the patient's medication, which was taken as usual on the day of the study. Results obtained were compared with 45 age, sex, and smoking matched controls.

The left ventricular ejection fraction was measured in the patients with congestive heart failure as follows: the patient's red cells were labelled in vivo by an injection of stannous pyrophosphate. Twenty minutes later, an injection of 740 MBq of technetium-99m pertechnetate was given. Data were acquired in the anterior and optimised left anterior oblique views with an Ohio Nuclear Series 100 gamma camera linked to a Nodecrest V70 computer. Sixteen 64 × 64 images were obtained during each cardiac cycle by an electrocardiographic gating technique. The left ventricular ejection fraction was calculated from the left anterior oblique view; the angle of this was carefully chosen to maximise the

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Table *Comparability of groups*

	Controls	*CHF*
Number	45	45
Age (years) median	58	62
range	(27–68)	(40–74)
Sex M.F	29 16	37.8

CHF, congestive heart failure

separation of the right and left ventricles. A degree of caudal tilt was used to increase the separation of the left atrium from the left ventricle.

Immediately before the left ventricular ejection fraction was measured venous blood samples were collected in a standard manner into a lithium heparin anticoagulant (10 units/ml) tube. The samples were immediately processed and assayed for plasma malondialdehyde-like material. Plasma lipid peroxide concentrations were estimated by Aust's spectrophotometric assay.[10] Absorbance was converted to concentration by an extinction coefficient of $1{\cdot}50 \times 10^5$ mol^{-1} cm^{-1}. The amount of malondialdehyde-like material is a measure of lipid peroxidation and its measure provides an estimate of free radical activity. Plasma thiol is an index of the oxidative status of the extracellular environment. Plasma thiol was estimated by the method described by Ellman.[11]

Results

The table shows the comparability of the patients with congestive heart failure and the controls. There was no difference between the two groups (χ^2 test).

Figure 1 shows the concentration (median (IQR)) of malondialdehyde-like material in both the control population and in patients with congestive heart failure (7·7 (6·9–9·2) *v* 9 (7·9–10 2) nmol/ml). The patients with congestive heart failure had significantly higher concentrations of malondialdehyde-like material ($p < 0{\cdot}01$, Mann-Whitney).

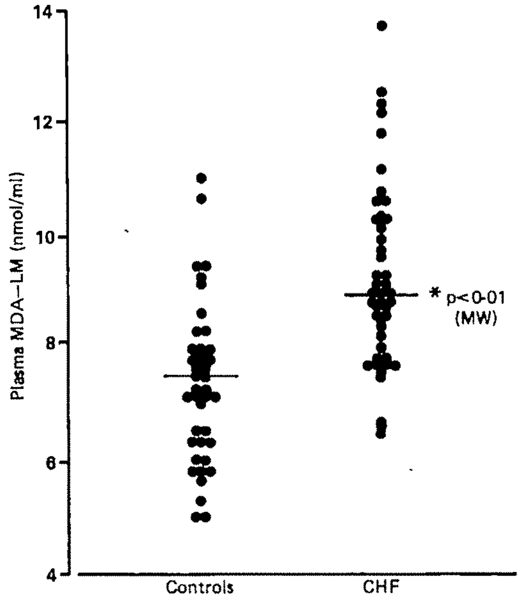

Figure 1 Plasma concentrations of malondialdehyde-like material (MDA-LM) in patients with congestive heart failure (CHF) and in controls.

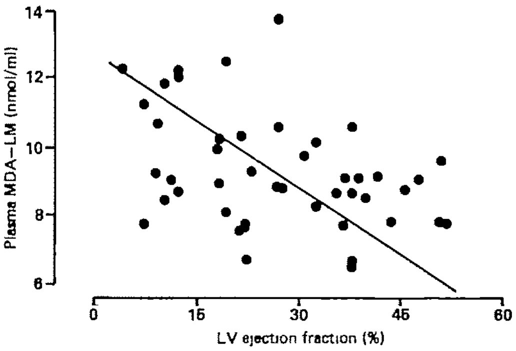

Figure 2 Plasma concentrations of malondialdehyde-like material (MDA-LM) and left ventricular (LV) ejection fraction in patients with congestive heart failure.

Figure 2 shows the left ventricular ejection fraction of the 45 patients plotted against the concentration of malondialdehyde-like material. There was a statistically significant inverse correlation between the two ($r = -0{\cdot}35$, $p < 0{\cdot}05$, Spearman rank). The higher the concentration of the malondialdehyde-like material the worse the left ventricular ejection fraction.

Figure 3 shows the concentration of plasma thiol (median (IQR)) in both the controls and patients with congestive heart failure (463 μmol/l (445–525) *v* 420 (379–480)). The patients with congestive heart disease had significantly lower concentrations of plasma thiol ($p < 0{\cdot}01$, Mann-Whitney).

Figure 4 shows the relation between left ventricular ejection fraction and plasma thiol concentration. Again there was a statistically significant correlation, this time positive ($r = 0{\cdot}39$, $p < 0{\cdot}01$, Spearman rank); as plasma thiol fell the left ventricular ejection fraction became worse.

Discussion

We found that there was an increase in lipid

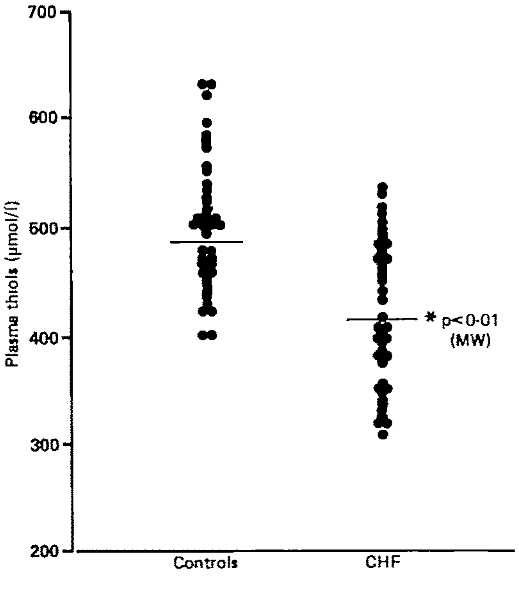

Figure 3 Plasma thiols in patients with congestive heart failure (CHF) and in controls

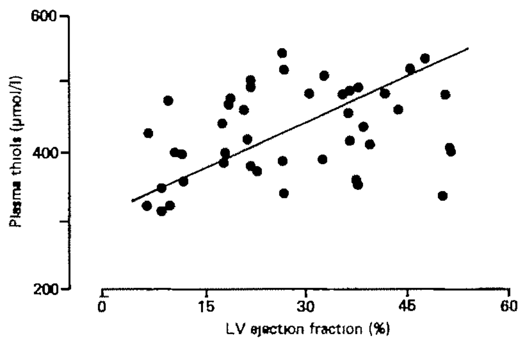

Figure 4 Plasma thiols and left ventricular (LV) ejection fraction in patients with congestive heart failure

peroxides in the blood of patients with congestive heart failure. Moreover, there was a significant negative correlation with left ventricular ejection fraction, which is one of the best predictors of survival in congestive heart failure.[12] Free radicals are unstable reactive chemical species produced during the course of normal metabolism that contain an unpaired electron. The half life of free radicals is measured in microseconds because they rapidly react with unoxidised adjacent molecules. They probably directly initiate tissue damage in several diseases where they are produced in excess.[13-15] The reactivity of free radicals precludes their direct measurement in humans except by the most complex techniques.[16] Their presence can be inferred, however, by their known effects, such as oxidation of polyunsaturated fatty acids. This is detected by the thiobarbituric acid test which detects the aldehyde products of peroxidised lipid and carbohydrates.[10] Recent advances in assay methods suggest that high performance liquid chromatography is a more sensitive and specific assay for malondialdehyde-like material; however, this project was already under way before the high performance liquid chromatographic assay was validated in our laboratory. Nevertheless, we have no reason to believe that artefactual results have been produced and the abnormal concentrations of malondialdehyde-like material accord with the plasma thiol results. We found that freezing and storing the samples produced very variable results. By assaying the samples immediately after venesection we believe we reduced the variability seen with the spectrophotometric assay. The plasma thiol estimation measured albumin thiol which decreased in the presence of free radical activity owing to oxidation of the sulphydryl group to disulphides.[17 18] The results of these tests support a theory that free radicals are involved in congestive heart failure.

We suggest therefore that oxygen free radicals are involved in the genesis and maintenance of congestive heart failure and there is theoretical support for this in published reports. Impairment of myocardial contractility or pressure or volume overload will all cause myocardial ischaemia, which in turn induces an increase in xanthine oxidase and xanthine and a decrease in the scavenging activity of superoxide dismutase and glutathione peroxidase.[19] Both these changes will lead to an increase in the generation of free radicals. The decrease in cellular pH during ischaemia will lead to formation of prostaglandins and leukotrienes. During their synthesis free radicals will be produced.[8] Leukotriene B_4 will further activate the polymorphonuclear leucocytes and increase secretion of neutrophil free radicals.[20] The compensatory mechanism of an increase in catecholamines in congestive heart failure also increases free radicals.[9] Free radicals themselves depress Ca^{2+} binding and uptake into sarcoplasmic reticulum[21]; this would lead to a decrease in cardiac contractility. Thus it is likely that free radicals actively promote the progression of congestive heart failure. Most of our patients had atherosclerosis underlying their congestive heart failure and the above mechanisms will contribute to the abnormalities detected. It would be of interest to study patients with congestive heart failure secondary to conditions such as a cardiomyopathy to see whether free radical products are also increased.

The development of treatments to reduce or prevent radical induced tissue injury may therefore be useful in congestive heart failure. There are two major classes of antioxidant: preventative antioxidants (for example, catalase, glutathione peroxidase, caeruloplasmin) and chain-breaking (radical-trapping) antioxidants (for example, vitamin E, vitamin C, reduced glutathione). Certain compounds can be classified as both preventative and chain-breaking antioxidants because they have both functions (for example, superoxide dismutase, β carotene). The angiotensin converting enzyme inhibitor, captopril, a well established drug used in the treatment of congestive heart failure, contains a sulphydryl group. Because one of the effects of sulphydryl-containing compounds is to scavenge free radicals, captopril may be a free radical scavenger. We have confirmed this both in vitro[22] and in humans.[23]

We showed that patients with congestive heart failure have evidence of increased free radical activity that correlates with the left ventricular ejection fraction, a measure of heart function linked to prognosis. It is likely that congestive heart failure causes myocardial ischaemia with free radical production. Free radicals cause myocyte dysfunction, exacerbating the impaired cardiac function and a vicious cycle is set in motion with the net result that cardiac function steadily deteriorates. Some drugs used in the treatment of congestive heart failure may be effective scavengers and such treatments should be further investigated.

We thank Dr Norman Kennedy, Department of Nuclear Medicine, Ninewells Hospital for his help with the left ventricular ejection fraction measurements and Dr G McNeill and Dr T Pringle for allowing us to study their patients

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Neuroendocrine activity in untreated heart failure

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Abstract

Neuroendocrine activity was studied in 60 consecutive untreated patients with dyspnoea and a clinical suspicion of heart failure. On the basis of the so-called Boston clinical criteria the diagnosis of heart failure was regarded as unlikely in 26 patients, possible in 15 patients, and definite in 19 patients. These groups were studied before any drug treatment was started and were compared with a control group of 69 healthy individuals. Plasma atrial natriuretic peptide concentration was clearly raised in patients with definite heart failure and slightly raised in patients with possible heart failure. Plasma adrenaline concentration was somewhat raised in patients with definite or possible heart failure, whereas plasma noradrenaline concentration was raised only in patients with definite heart failure. Plasma renin activity was not increased in any of the patient groups and plasma aldosterone concentration was slightly increased only in patients with definite heart failure. In the total patient series there were significant correlations between plasma atrial natriuretic peptide concentration and markers of the severity of left ventricular dysfunction.

There was some evidence of neuroendocrine activation in untreated heart failure: plasma concentrations of atrial natriuretic peptide and catecholamines were increased but the renin-angiotensin-aldosterone system showed little or no activation.

The basic disturbance in heart failure is a defect in left ventricular pump function which results in inadequate blood flow to peripheral tissues. In advanced congestive heart failure, complex neuroendocrine mechanisms are activated in an attempt to compensate for the decreased cardiac output. These responses include release of atrial natriuretic peptide from cardiac myocytes,[1-3] activation of the sympathetic nervous system,[4 5] and activation of the renin-angiotensin-aldosterone system.[6-8]

Most studies of the hormonal changes in heart failure have included patients treated with diuretics; there is little information on the activation of the neuroendocrine system in untreated heart failure,[9-12] especially on concentrations of atrial natriuretic peptide. We studied neuroendocrine activation in patients in whom the diagnosis of heart failure was suspected for the first time and in whom treatment for the condition had not been started. We used the Boston diagnostic criteria[13] to confirm the clinical diagnosis of heart failure.

Patients and methods

PATIENTS

We studied 88 patients (37 men and 51 women) with a clinical suspicion of previously unrecognised heart failure and 82 controls (36 men and 46 women), all aged 45–74 years. Patients were identified by 32 primary health care physicians working in community health centres in a defined area in eastern Finland. These physicians had agreed to refer to the university clinic all patients who had presented with symptoms or signs suggestive of heart failure and in whom this condition had not been previously diagnosed. Patients with acute pulmonary oedema complicating myocardial infarction were not included. Those 24 patients who had severe symptoms were referred immediately and studied on the day of referral, whereas the remaining 64 patients with milder symptoms were examined within two weeks of their visit to the primary health care centre. A detailed description of the patient series has been published elsewhere.[14]

Twenty eight patients were excluded from hormone analyses: 21 because of current treatment with digitalis, diuretics, angiotensin converting enzyme inhibitors, or sympathomimetic drugs; three because of severe respiratory failure caused by pulmonary disease or kyphoscoliosis, and four because of other diseases with indications for immediate treatment such as acute bronchitis, acute fibrosing alveolitis, diabetic ketoacidosis, or pulmonary embolism. Thus 60 patients (23 men and 37 women) comprised the final patient population. All of them had dyspnoea or fatigue or both. Seven patients had atrial fibrillation and 53 were in sinus rhythm.

We identified 300 candidates for the control group by a random population sample of 45–74 year old inhabitants in the survey area. A mailed questionnaire was used to exclude persons with previously diagnosed heart failure, coronary heart disease, hypertension, arrhythmias, or other disabling conditions. Eighty eight persons were thus selected from the initial sample, but 19 of them were excluded after the study visit. The reasons for exclusion

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were bronchial asthma, coronary heart disease (15 cases), gastric carcinoma, hypertrophic cardiomyopathy, and Parkinson's disease. Thus the control group comprises 69 persons without any symptomatic cardiac or pulmonary disease or other obvious disease.

All examinations at the Kuopio University Central Hospital were performed before drug treatment for heart failure was started. The study was carried out from 1 June 1986 to 3 May 1988 and the patient and control series were examined in parallel over the study period. The study protocol was approved by the ethics committee of the University of Kuopio. Informed consent was obtained from each patient and control.

Methods

Clinical examination

One of us (JR) carried out the clinical examination and interpretation of conventional chest radiographs on all study subjects. The examination included a questionnaire on the patient's history of previous diseases and use of drugs. At the physical examination special attention was paid to signs of heart failure, such as the third heart sound, rales or wheezing on lung auscultation, raised jugular venous pressure, liver enlargement, or leg oedema. Weight and height were measured in light indoor clothing and body mass index was calculated as weight in kilograms per height in metres squared. A patient was considered to be non-obese if body mass index was <27 kg/m^2 and obese if body mass index was ⩾27 kg/m^2. Blood pressure was measured in recumbent individuals with a sphygmomanometer after five minutes of supine rest and the average of two measurements at an interval of two minutes was used. Heart rate was obtained from the resting electrocardiogram and relative heart volume was estimated from the chest *x* ray according to the method of Jonsell.[15]

Diagnostic classification

Information from clinical and radiographic examinations was used in the diagnostic classification of patients by a modification of the so-called Boston diagnostic criteria for heart failure.[13 14] In this scoring system points were given in three categories: for features in the history, for physical signs, and for radiographic signs suggestive of the presence of heart failure. Points were given in the first category for symptoms of dyspnoea and fatigue; in the second category for tachycardia, raised jugular venous pressure, lung rales or wheezing, and third heart sound; and in the third category for abnormal filling pattern of pulmonary veins, enlarged heart silhouette, pleural effusion, and evidence of interstitial or alveolar pulmonary oedema. A maximum of four points was allowed in each of the three categories, so a maximum score of 12 points was possible. Group 1 consisted of patients with a score of 0–4 points, defined as "unlikely to have heart failure". Patients with a score of 5–7 points were defined as having "possible heart failure" (group 2). Patients with a score of 8–12 points were defined as having "definite heart failure" (group 3).

A patient was considered to have coronary heart disease when one of the following criteria was fulfilled: (*a*) the patient had a history of myocardial infarction; (*b*) the patient had angina pectoris by the Rose questionnaire,[16] or (*c*) ischaemic changes were seen in the resting electrocardiogram (Minnesota codes 1·1–1·3, 4·1–4·3, 5·1–5·3, or 7·1 (Whitehall criteria)), including Q–QS abnormalities, ST segment depressions, T wave changes, or left bundle branch block.[17] A patient was considered to have hypertension if the systolic blood pressure was ⩾160 mm Hg or the diastolic blood pressure was ⩾95 mm Hg during supine rest or if the patient had been receiving drug treatment for hypertension.

Echocardiography

M mode echocardiography was performed with a sector electronic scanning type ultrasound diagnostic system (Toshiba (Sonolayer Model SSH-40A, Japan) and a 2·4 MHz transducer (Toshiba PSA-24B, Japan). Subjects were examined in the left lateral decubitus position. Cross sectional scans were used to position the M mode recordings just below the edge of the anterior mitral leaflet. M mode echocardiograms were recorded on photosensitive paper at a paper speed of 100 mm/s. Measurements were made from the paper recordings according to the recommendations of the American Society of Echocardiography[18] with a x-y digitiser (resolution 0·1 mm) interfaced to a computer.[19] Five consecutive or near consecutive cardiac cycles were measured and the means of the values were recorded. Echocardiographic measurements were carried out on all study subjects by the same investigator (JR). The following variables were recorded: diameter of the left atrium, left ventricular end diastolic diameter, and left ventricular end systolic diameter. Fractional shortening and peak rate of increase in left ventricular diameter during diastole (used as an index of left ventricular relaxation) were calculated by the computer.

Exercise testing

A bicycle ergometer exercise test with noninvasive gas exchange analysis was carried out on those patients who did not have dyspnoea at rest. The exercise test was performed by patients sitting on an electrically braked bicycle ergometer. The workload was continuously increased by 15 W every minute until the patient became exhausted. The rate of oxygen consumption was determined by analysing the expired gas breath by breath during exercise. A Medical Graphics Corporation CAD/Net system 2001 analyser was used in the analysis.[20] The average rate of oxygen consumption during the last 20 seconds of exercise was taken as peak oxygen consumption.

Hormone assays

Blood samples for homone analyses were taken in the early morning hours after an overnight fast. A Teflon cannula (Venflon 18 G/1·2 mm, Sweden) was positioned in a large antebrachial vein, and patients rested in the supine position for at least 30 minutes. Blood was then drawn into prechilled EDTA tubes placed on ice. Plasma was separated at 4°C within 20 minutes, frozen immediately, and stored at −70°C until assay.

Radioimmunoassay techniques were used to measure plasma atrial natriuretic peptide concentration and renin activity as previously described.[1 21] Plasma aldosterone was measured by a commercial radioimmunoassay kit (Abbott Laboratories, Chicago, Illinois). Plasma concentrations of adrenaline and noradrenaline were assessed by high performance liquid chromatography with electrochemical detection.[22] The investigators in charge of hormone assessments (IT and FF) were not aware of the clinical condition of the individuals studied.

Statistical analysis

Results are expressed as means (SEM) and medians. SPSS programmes (Statistical Package for the Social Sciences, Chicago, USA) were used for statistical analyses. One way analysis of variance was used to detect overall differences between group means of normally distributed variables. If p value was $\leqslant 0{\cdot}05$ in one way analysis of variance, Student's *t* test for unpaired data was used in further comparisons. Hormone values showed a skewed distribution, and therefore the non-parametric Mann-Whitney test was used to compare hormone values. Frequency differences were tested by the χ^2 test. p Values of $< 0{\cdot}05$ were regarded as significant. Correlation analyses were carried out by standard linear regression techniques available in the SPSS programmes; correlations were considered significant at $p < 0{\cdot}01$.

Results

CLINICAL CHARACTERISTICS

Most patients were in New York Heart Association functional class I–III, and thus symptoms suggestive of heart failure were in general mild or moderate (table 1). However, 10 patients (53%) in group 3 belonged to functional class IV. Twenty six patients (six men and 20 women) were classified "unlikely to have heart failure" (group 1). This shows that primary health care diagnosis of heart failure was more often incorrect in women than in men ($p < 0{\cdot}01$).[14] Obesity was common in all patient groups. There were signs of volume overload such as leg oedema, liver enlargement, or increased jugular venous pressure in four patients (15%) in group 1, six (40%) in group 2, and 13 (68%) in group 3.

Most patients had evidence of either coronary heart disease or hypertension and some were taking drugs for angina pectoris. According to the criteria used in this study, some of the control subjects also had hypertension as judged by a single blood pressure measurement. Coronary heart disease was more common in group 2 than in group 1. Hypertension was significantly more common in group 3 than in the control group or group 1, whereas no significant differences in frequencies of hyper-

Table 1 Some clinical characteristics, cardiac diseases, and use of cardiac drugs in control and patient groups

	Controls *(n = 69)*	*Group 1* *(n = 26)*	*Group 2* *(n = 15)*	*Group 3* *(n = 19)*
Characteristics				
Sex (male/female)	29/40	6/20	4/11	13/6‖
Age (yr)	61 (1)	59 (1)	63 (2)§	61 (2)
Heart rate (beats/min)	65 (1)	68 (2)	80 (6)‡	91 (4)‡§
Systolic blood pressure (mm Hg)	150 (3)	148 (4)	156 (8)	154 (6)
Diastolic blood pressure (mm Hg)	84 (1)	88 (1)	86 (3)*	90 (2)†
Weight (kg)	72 (2)	75 (1)	70 (2)	78 (3)
Body mass index (kg/m²)	26·2 (0·5)	29·3 (0·8)†	28·2 (1·6)	27·7 (1·2)
Relative heart volume (ml/m²)	430 (10)	420 (20)	550 (40)‡¶	670 (30)‡¶
NYHA class (n) (%)				
I		6 (23)		
II		15 (58)	7 (47)	3 (15)
III		4 (15)	7 (47)	6 (32)
IV		1 (4)	1 (6)	10 (53)
Cardiovascular disorders (n) (%)				
Coronary heart disease		15 (58)	9 (60)	16§ (80)
Hypertension	34 (42)	11 (42)	9 (60)	14*§ (70)
Valvar heart disease			2 (13)	2 (10)
Cardiac drugs (n) (%)				
β Blocker		4 (15)	2 (13)	6 (30)
Calcium antagonist			1 (7)	2 (10)
Long acting nitrate		3 (12)	2 (13)	4 (20)

Except where indicated data are given as mean (±SEM). NYHA class, New York Heart Association functional class Hypertension was defined as a single casual blood pressure measurement ≥160/95 mm Hg *$p < 0{\cdot}05$, †$p < 0{\cdot}01$, ‡$p < 0{\cdot}001$, any patient group *v* control group, §$p < 0{\cdot}05$, ‖$p < 0{\cdot}01$, ¶$p < 0{\cdot}001$, group 2 or 3 *v* group 1 (Student's *t* test or χ^2 test).

Table 2 Important biochemical variables (mean (SEM)) in control and patient groups

	Controls *(n = 69)*	*Group 1* *(n = 26)*	*Group 2* *(n = 15)*	*Group 3* *(n = 19)*	*p Value*
Blood hematocrit	0·40 (0·0)	0·40 (0·01)	0·41 (0·01)	0·40 (0·01)	0·912
Serum ACE (μmol/min/l)	13·9 (0·5)	14·7 (0·9)	13·3 (1·0)	13·0 (1·1)	0·524
Serum albumin (g/l)	44 (0)	44 (1)	45 (1)	40 (1)†‡	0·001
Serum creatinine (μmol/l)	84 (1)	79 (2)	83 (3)	107 (7)†§	<0·001
Serum potassium (mmol/l)	4·3 (0·0)	4·2 (0·1)	4·3 (0·1)	4·4 (0·1)	0·241
Serum sodium (mmol/l)	145 (0)	145 (1)	145 (1)	143 (1)*	0·027

ACE, angiotensin converting enzyme. p Value by one way analysis of variance: *$p < 0{\cdot}05$ and †$p < 0{\cdot}01$ any patient group *v* control group; ‡$p < 0{\cdot}05$, §$p < 0{\cdot}01$, group 3 *v* group 1 (Student's *t* test)

Table 3 Echocardiographic variables and peak rate of oxygen consumption in the control group and patient groups (mean (SEM))

Variable	*Control*	*n*	*Group 1*	*n*	*Group 2*	*n*	*Group 3*	*n*	*p Value*
Fractional shortening (%)	34 (1)	63	33 (1)	23	28 (2)*§	13	21 (2)‡¶	17	<0 001
Left atrial diameter (mm)	33 (1)	63	35 (1)	23	36 (1)*	13	41 (1)‡¶	17	<0 001
LV end diastolic diameter (mm)	50 (1)	63	49 (1)	23	54 (1)*‖	13	59 (2)‡¶	17	<0 001
LV end systolic diameter (mm)	33 (1)	63	33 (1)	23	39 (2)†‖	13	45 (2)‡¶	17	<0 001
Peak rate of increase in LV diameter (cm/s)	12 2 (0 2)	60	10 8 (0 5)†	21	10 0 (1 0)*	13	8 0 (0 8)‡‖	16	<0 001
Peak Vo_2 (ml/kg/min)	26 0 (0 7)	69	20 7 (0 8)‡	23	16·9 (2·0)‡	13	14 9 (2·0)‡‖	7	<0 001

LV, left ventricular. Vo_2, rate of oxygen consumption. p Value by one way analysis of variance: *p < 0 05, †p < 0·01, ‡p < 0 001, groups 1–3 *v* control group, §p < 0 05, ‖p < 0 01, ¶p < 0 001, group 2 or 3 *v* group 1 (Student's *t* test).

Table 4 Comparison of plasma hormone values in control group and patient groups (mean (SEM) and medians (in parentheses))

	Control	*n*	*Group 1*	*n*	*Group 2*	*n*	*Group 3*	*n*
ANP (pg/ml)	51 (4) (50)	69	56 (6) (52)	26	130 (36)†§ (74)	15	267 (42)‡‖ (254)	19
Adrenaline (nmol/l)	0 30 (0 03) (0 24)	66	0 33 (0 04) (0 28)	25	0 51 (0 10)* (0 41)	14	0 41 (0 05)* (0 43)	17
Noradrenaline (nmol/l)	2 04 (0 10) (1 90)	66	2 12 (0 17) (1 86)	25	2 45 (0 29) (2 21)	14	2 63 (0 28)* (2 52)	17
Aldosterone (pmol/l)	130 (7) (120)	69	160 (15) (148)	26	146 (24) (137)	15	194 (132)* (162)	18
PRA (ng/ml/h)	2 7 (0 2) (2 3)	69	2 4 (0 2) (2 2)	26	3 3 (0 5) (2 7)	15	2 9 (0 6) (2·4)	19

ANP, atrial natriuretic peptide; PRA, plasma renin activity *p < 0 05, †p < 0 01, ‡p < 0 001 for group 1, 2, or 3 *v* control groups, §p < 0 01, |p < 0 001, for group 2 or 3 *v* group 1 (Mann–Whitney non-parametric test).

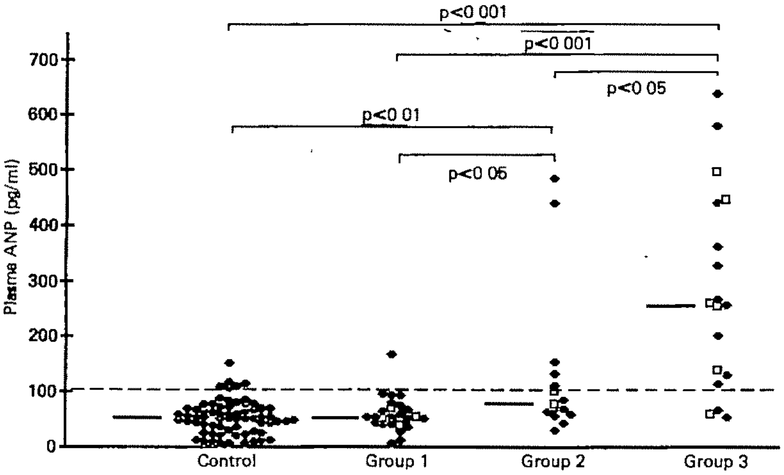

Figure 1 Plasma concentrations of atrial natriuretic peptide (ANP) in patients and controls. Group 1, heart failure unlikely; group 2, possible heart failure; and group 3, definite heart failure, according to the Boston classification. Open symbols indicate patients receiving β blockers. p Values indicate significance in the non-parametric test (Mann Whitney) Solid bars show medians; the dotted line represents the upper limit of the 95% confidence interval for values in the control group.

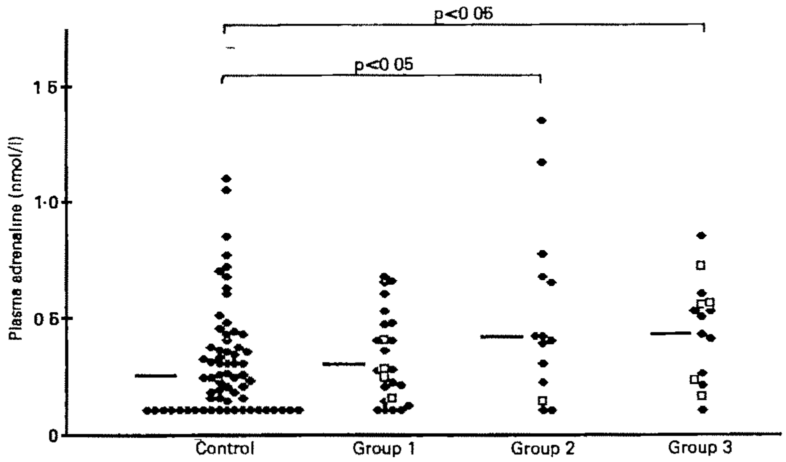

Figure 2 Plasma adrenaline concentrations in patients and controls (1 nmol/l = 183·2 pg/ml). See legend to figure 1 for an explanation of the groups and symbols.

tension were seen between group 1, group 2, and the control group. The serum creatinine concentration was higher in group 3 than in any other study group and serum sodium concentration was lower in group 3 than in the control group (table 2). In addition, the serum albumin concentration was lower in group 3 than in the control group or in group 1. No significant differences were seen in haematocrit between the study groups.

ECHOCARDIOGRAPHY AND EXERCISE TESTING

The left atrial and left ventricular diameters were greater and fractional shortening and peak rate of increase in left ventricular diameter were smaller in group 3 than in the control group or in group 1 (table 3). The dimensions of the cardiac chambers were greater and fractional shortening was smaller in group 2 than in the control group or in group 1. These data indicate that both left ventricular systolic and diastolic function were impaired in groups 2 and 3. There was no difference in indices of left ventricular systolic function between group 1 and the control group. On the other hand, the peak rate of increase in left ventricular dimension was lower in group 1 than in the control group, which suggests that left ventricular diastolic function was also impaired in group 1. Furthermore, the peak rate of oxygen consumption in the exercise test was greater in each patient group than in the control group and it was lower in group 3 than in group 1. The results of the echocardiographic and exercise measurements were essentially the same when men and women were analysed separately.

PLASMA HORMONES

Plasma atrial natriuretic peptide concentration was higher in group 3 than in any other study group and it was higher in group 2 than in the control group or group 1 (table 4, fig 1). Both plasma adrenaline and noradrenaline concentrations were somewhat higher in group 3 than in the control group but they were not higher in group 3 than in group 1 or group 2 (figs 2 and 3). Plasma aldosterone concentration showed a wide range of variation in all study groups (fig 4). There was no significant difference between the study groups in plasma renin activity, which was considerably increased in only four patients (fig 5).

There were no significant differences in plasma hormone values between men and women, and no significant differences between non-obese and obese persons either in the entire patient population or within any of the study groups. The results were essentially the same when patients treated with β blockers, calcium antagonists, or long acting nitrates were excluded separately or altogether from the analysis. The results also remained unchanged when those controls who were defined as having hypertension were not included. Plasma atrial natriuretic peptide concentration was higher in patients who had signs of volume overload than in patients who had none of these signs (192 (23) pg/ml *v* 113 (35) pg/ml, $p < 0{\cdot}01$ (all patients included)). However, even when only those patients in whom no signs of volume overload were seen were included in the analysis, plasma atrial natriuretic peptide concentration was still higher in group 3 than in group 1 (297 (81) pg/ml *v* 53 (7) pg/ml, $p < 0{\cdot}01$). We found no significant differences between the study groups for any other hormones which are associated signs of volume overload.

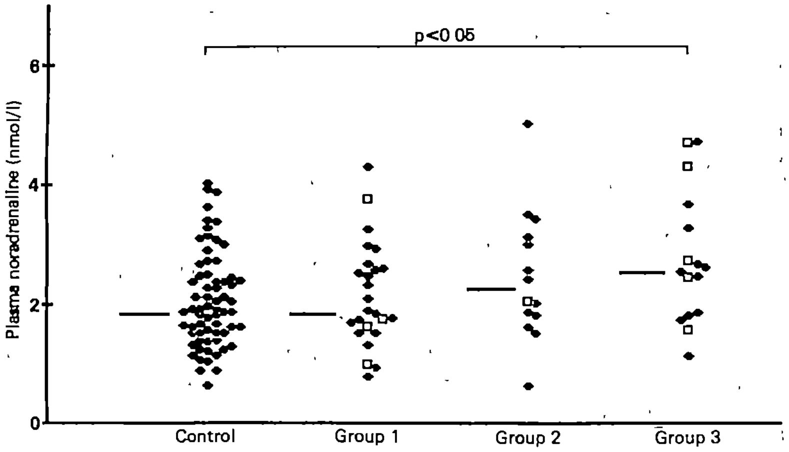

Figure 3 Plasma noradrenaline concentrations (1 nmol/l = 169·2 pg/ml) in patients and controls. See legend to fig 1 for an explanation of the groups and symbols.

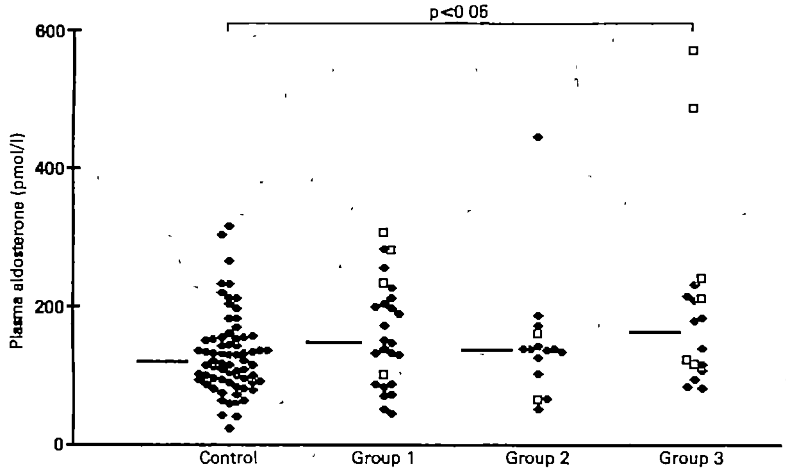

Figure 4 Plasma aldosterone concentrations in patients and controls subjects. See legend to fig 1 for an explanation of the groups and symbols.

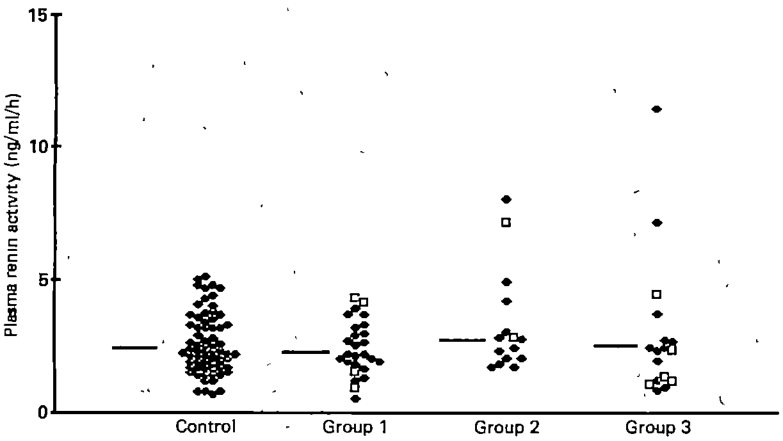

Figure 5 Plasma renin activities in patients and controls. See legend to fig 1 for an explanation of the groups and symbols.

Table 5 shows the correlations of plasma hormone values with each other and with some other selected variables. All patients were included in these linear regression analyses. There was a positive correlation between plasma atrial natriuretic peptide, adrenaline, and noradrenaline concentrations. Plasma atrial natriuretic peptide concentration was also correlated positively with heart rate, relative heart volume, New York Heart Association functional class, and with left atrial and ventricular dimensions determined by echocardiography. Plasma atrial natriuretic peptide concentration was negatively correlated with fractional shortening, peak rate of increase in left ventricular diameter, and peak rate of oxygen consumption.

In group 3, there was a statistically significant inverse correlation between plasma atrial natriuretic peptide concentration and peak rate of increase in left ventricular diameter ($r = -0{\cdot}603$, $p < 0{\cdot}01$) and with peak rate of oxygen consumption ($r = -0{\cdot}966$, $p < 0{\cdot}01$). No other significant correlations were found within this group between plasma hormone values and the variables listed in table 5. We found no significant correlations between any of the plasma hormone measurements in the controls, but there was a weak inverse correlation between plasma adrenaline concentration and left ventricular end diastolic and end systolic diameters ($r = -0{\cdot}287$, $p < 0{\cdot}01$ and $r = -0{\cdot}289$, $p < 0{\cdot}01$, respectively).

We assessed the possible usefulness of plasma atrial natriuretic peptide measurement as a diagnostic test in confirming the presence or absence of "definite heart failure" by the Boston classification by using the upper limit of the 95% confidence interval in the control group (101 pg/ml) as the cut off value. This cut-off value had a sensitivity of 83% and a specificity of 85% in identifying patients belonging to group 3—that is, patients with "definite heart failure" (fig 1). Furthermore, if the plasma concentration of atrial natriuretic peptide was above the cut off level, the probability that the patient belonged to group 3 was 71% (positive predictive value) and if the

Table 5 Correlation coefficients of hormone values with each other and with other selected variables, all patients included

Variable	*ANP*	*Adrenaline*	*Noradrenaline*	*Aldosterone*	*PRA*
ANP	1 000	0 361*	0 466†	0 149	0 190
Adrenaline	0 361*	1 000	0 393*	−0 090	−0 238
Noradrenaline	0 466†	0 393*	1 000	−0 262	−0 092
Aldosterone	0 149	−0 090	0 262	1 000	0·153
PRA	0 190	−0 238	−0 092	0 153	1 000
Heart rate	0 452†	0 183	0 242	0 054	0 118
Relative heart volume	0 616†	0 274	0 321	0 128	0 073
NYHA class	0 500†	0 136	0 124	0 138	0 140
Fractional shortening	−0 580†	−0 230	−0 288	−0 069	0 304
Left atrial dimension	0 341*	0·016	0 095	−0 113	0 009
LV end diastolic diameter	0 481†	−0 073	0 026	0 286	0 099
LV end systolic diameter	0 581†	0 080	0 141	0 080	0 240
Peak rate of increase in LV diameter	−0 448*	−0 093	−0 174	0 056	−0 337
Peak rate of oxygen consumption	−0 469*	−0 152	−0 339	−0 330	−0 244

ANP, atrial natriuretic peptide, LV, left ventricular; NYHA class, New York Heart Association functional class, PRA, plasma renin activity Correlation coefficients were obtained by linear regression analysis, $*p < 0\ 01$, $\dagger p < 0\ 001$

plasma atrial natriuretic peptide concentration was equal to or below the cut off level, the probability that the patient did not belong to group 3 was 92% (negative predictive value). Three patients who had been classified as group 3 had plasma atrial natriuretic peptide concentrations below 101 pg/ml (fig 1), but two of them had been receiving treatment with calcium antagonists and one with long acting nitrates. On the other hand, two patients belonging to group 2 had plasma atrial natriuretic peptide concentrations considerably above the cut off value; one had aortic valve stenosis and incompetence and the other had aortic valve incompetence. Just one of 21 patients with plasma atrial natriuretic peptide of > 101 pg/ml was classified as group 1 and that patient had atrial fibrillation.

Discussion

This study on the neuroendocrine activation in newly diagnosed heart failure showed that the concentration of plasma atrial natriuretic peptide was raised and sympathetic nervous activity was already increased before the start of treatment, whereas the renin-angiotensin-aldosterone system was not activated at this stage.

Since the discovery of atrial natriuretic peptide by deBold *et al*,[23] the peptide has been a subject of intensive research. It is now well known that atrial natriuretic peptide is stored in both the atrial and ventricular cardiocytes[24 25] and is released from the cardiocytes in response to stretching of the atrial tissue,[26 27] expansion of circulating blood volume,[28] or increased atrial contraction frequency.[29] Previous studies have shown, furthermore, that the plasma concentration of atrial natriuretic peptide is raised in patients with chronic heart failure (during drug treatment), and that the rise is proportional to the increase in atrial pressure.[3] In our study the plasma atrial natriuretic peptide concentration was raised in all patients with definite heart failure who were not treated with vasodilators. Furthermore, in our untreated patients the plasma concentration of atrial natriuretic peptide correlated with the severity of dyspnoea, with peak oxygen consumption, with radiographic heart volume, and with echocardiographic indicators of the severity of left ventricular dysfunction. Although no haemodynamic data were available on our patients with heart failure, increased atrial pressure (or stretch) is the most likely mechanism underlying the raised plasma atrial natriuretic peptide concentration.

Several studies have shown that sympathetic nervous activity, as judged by measurement of plasma noradrenaline concentration, is increased in patients with heart failure during treatment with diuretics.[30–32] However, studies of sympathetic nervous activity in untreated heart failure have been contradictory. In a recent study, plasma noradrenaline concentration was not raised in patients with mild heart failure from whom cardiac medication had been withdrawn one week before the study.[10] Whereas plasma noradrenaline concentrations were raised in untreated patients with moderately severe[9] or severe heart failure[12] and also in patients with asymptomatic left ventricular dysfunction.[33] In our study, plasma adrenaline and noradrenaline concentrations were both significantly higher in patients with "definite" heart failure than in healthy controls. Thus our results accord with activation of the sympathetic nervous system early in the natural course of heart failure.

It is generally accepted that the activity of the renin-angiotensin-aldosterone system is increased in patients with advanced chronic heart failure treated with diuretics.[34 35] On the other hand, some previous studies based on small series of patients suggested that the renin angiotensin-aldosterone system would not be activated in patients with heart failure who have not received treatment with diuretics.[11 12 14] The results of the present study confirm that activation of this system is uncommon in untreated heart failure. However, because these findings apply to the activity of the renin-angiotensin-aldosterone system in circulating blood only they do not exclude the possibility that the tissue renin-angiotensin systems could be altered in heart failure.

We found that plasma atrial natriuretic peptide concentration was higher in those patients in whom there was a definite diagnosis of heart failure according to the Boston classification and that it was uncommon in patients who proved not to be in heart failure. We are cautious about drawing definite conclusions from this cross sectional study, but our findings do suggest that the measurement of plasma atrial natriuretic peptide might be helpful in the diagnostic evaluation of patients with suspected heart failure and that this measurement could be particularly useful in excluding heart failure.

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Balloon dilatation of the aortic valve in the fetus: a report of two cases

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Abstract

Because they had irreversible damage to the left ventricular myocardium none of 12 patients with critical aortic stenosis diagnosed prenatally survived after postnatal treatment. This experience prompted three attempts at intrauterine balloon dilatation of the aortic valve in two fetuses with this condition. On each attempt the balloon catheter was successfully delivered to the left ventricle. In the first fetus the aortic valve was not crossed and the fetus died the next day. In the second fetus the balloon was correctly positioned across the aortic valve and inflated in the valve ring. After delivery, a further balloon angioplasty was performed; this relieved the stenosis but the patient died five weeks later from persisting left ventricular dysfunction related to endocardial fibroelastosis.

Balloon angioplasty is feasible in fetal life but the prognosis depends on the ability of the relief of stenosis to limit, prevent, or allow regression of left ventricular damage before delivery.

The mildest forms of congenital aortic stenosis may become haemodynamically important only in late adult life when calcification becomes a prominent feature whereas the most severe forms are life threatening in infancy. In the neonate mortality is high and left ventricular dysfunction with endocardial fibroelastosis is common. Even when the obstruction to the left ventricular outflow tract is relieved the left ventricle often fails to maintain cardiac output.

Recently, it has become possible to detect both aortic stenosis and the severer forms of endocardial fibroelastosis in fetal life. In our unit, 28 fetuses were identified as having aortic stenosis alone (two cases) or aortic stenosis with endocardial fibroelastosis (26 cases). In two of the 12 mothers who elected to continue the pregnancy there was an intrauterine death. None of the 10 livebirths survived; only four survived long enough for treatment by balloon dilatation of the aortic valve. In addition, we saw another prenatal feature that influenced the outcome. In four of the 28 fetuses, the left ventricle failed to grow normally as gestation advanced and the left ventricle became hypoplastic which made the neonate unsuitable for relief of aortic valve obstruction.[1]

Balloon dilatation is a well established technique for the relief of pulmonary or aortic stenosis in children.[2 3] Its efficacy in the newborn is being compared with that of surgical valvotomy.[4] We attempted balloon dilatation in the fetus in an attempt to improve the dismal prognosis for this condition by relieving obstruction to the aortic valve before irreversible left ventricular damage had developed and to try to prevent the growth failure that we had seen. We report our experience in two fetuses in whom balloon dilatation of the aortic valve was attempted.

Patients and methods

Both patients were referred to the Department of Perinatal Cardiology after a four chamber view of the heart in the local hospital indicated an abnormality. They were examined by an Advanced Technical Laboratories Mark 4 sector scanner and a Hewlett Packard 77020A phased array scanner with 5 MHz transducers. Both machines can be used for Doppler evaluation of intracardiac velocities and the Hewlett Packard 77020A can be used for colour flow mapping.

The parents were extensively counselled about the experimental nature of the procedures to be attempted. The therapeutic procedures were performed in the Fetal Medicine Unit at Guy's Hospital with an Acuson 128 ultrasound system for visualisation of the needle course and manipulation of the guide wires and balloon catheters. Eighteen gauge transabdominal chorionic villus sampling needles were used (Rockett, London). For needle puncture of the umbilical cord and cardiac chambers we used a freehand ultrasound guided method adapted from the technique first described by Daffos *et al*.[5] The maternal skin was infiltrated by local anaesthetic before each needle insertion. Intrauterine and intracardiac pressures were measured by a sterile system of fluid-filled tubing connected from the hub of the needle via a solid state transducer to a Siemans Mingograf by a previously described method.[6] In the first procedure we used a USCI coronary balloon catheter, diameter 2·5 mm when inflated. In the second case a 3·5 mm diameter balloon was custom made by NuMed.

CASE 1

This 23 year old woman (para 2) was initially referred at 22 weeks' gestation. The left ventricle was of normal size for the gestation but was contracting poorly. There was little discernible forward flow into the left ventricle or aorta. The left ventricular wall showed increased echogenicity. Colour flow mapping showed a patent foramen ovale. The parents were advised of the likely poor prognosis but the mother elected to continue the pregnancy. A repeat scan at 28 weeks' gestation showed that the left ventricle had not changed in size and was therefore small for the gestation by this time. There was no flow detectable in the ascending aorta and the atrial septum was now closed. The intrauterine procedure took place a few days later. The mother was sedated with intravenous pethidine. The fetal position was initially unfavourable with the spine anterior, but spontaneous fetal movement resulted in a more suitable position with the cardiac apex positioned laterally about an hour later. On the first needle insertion, the right ventricle was entered and a pressure tracing recorded. The needle was then withdrawn and the left ventricle entered through the left ventricular free wall. The balloon catheter was passed down the needle but the guide wire could not be made to cross the aortic valve. At this time at one point, the needle crossed the aortic valve. We thought that the route of approach was not sufficiently direct so a new needle insertion was attempted. This entered the heart at the apex and in line with the origin of the aorta. However, the guide wire was repeatedly deflected off the aortic valve to pass retrogradely through the mitral valve. Three episodes of fetal bradycardia occurred during the procedure; these were reversed with intracardiac isoprenaline. The attempt was considered to have failed and therefore was abandoned at this stage. The fetus was active and the heart was in sinus rhythm at the end of the procedure but death occurred during the next 24 hours.

Postmortem examination showed a single puncture mark on the anterior chest wall. There was 7 ml of blood in the left pleural cavity and 3 ml in the right. There was no blood in the pericardial cavity. The heart showed a moderate degree of left ventricular hypoplasia, a small stenotic mitral valve, and endocardial fibroelastosis of the left ventricle. The ascending aorta was small for gestational age. The valve was formed by a thin but complete membrane that had been raggedly torn, apparently during the interventional procedure and not at necropsy. The foramen ovale was not patent.

CASE 2

A 41 year old woman (para 2) was initially referred at 30 weeks' gestation. A normal fetal karyotype had been found on chorionic villus sampling at nine weeks' gestation. At a routine scan in the local hospital at 18 weeks' gestation, the four chamber view was passed as normal. The second scan at 30 weeks was to check placental position but the fetal heart seemed to be abnormal and the patient was referred to Guy's Hospital. The left ventricle was poorly contracting and thickwalled with increased echogenicity of the lining. There was, however, some forward flow through the mitral valve and the atrial septum was patent. The aortic valve seemed thickened and restricted in motion with the velocity of flow increased to 150 cm/s.

The first interventional procedure took place a week later at 31 weeks' gestation. The fetal orientation was favourable from the start such that a direct approach from the apex could be made on the first attempt. A guide wire was advanced through the needle and across the aortic valve under direct view. The balloon catheter was then inserted and inflated. The balloon, however, seemed to be in the left ventricular outflow tract and not in the valve orifice itself when inflation took place. Retrospective review of the videotape recorded at this time confirmed this. The balloon burst in situ, and when it was being withdrawn through the needle it impacted on the edge of the needle and was torn from the main body of the catheter. The needle and the portion of catheter within it were then withdrawn as one. The fetal heart remained in sinus rhythm throughout. No change in flow could be detected across the aortic valve after the procedure and the attempt was deemed unsuccessful. Subsequently the balloon and wire could be seen on ultrasound examination to be impacted between the left atrium and the septal left ventricular wall below the outflow tract. It was not causing any obstruction.

A second attempt was made 10 days later at 33 weeks' gestation. The left ventricular apex was entered on the second needle placement. A guide wire was entered through the needle and passed easily across the aortic valve. After we established that the valve could be crossed with the guide wire the wire was withdrawn and the custom made balloon catheter was then inserted. It was inflated twice within the valve orifice. The catheter and needle were then removed simultaneously. The fetal heart rate was normal throughout except for a transient bradycardia at balloon inflation that did not require treatment. Fetal movement did not interfere with the procedure. The technical success of the procedure appeared to be confirmed by an improvement in aortic flow shown by Doppler echocardiography; the velocity of flow fell from 150 cm/s to 120 cm/s.

One week later, the mother went into spontaneous labour and was delivered in the local hospital. The neonate was male, had Apgar scores of 7 and 9 at 1 and 5 minutes and weighed 2·98 kg. He was transferred to Guy's Hospital on facial oxygen and a prostaglandin infusion. The Doppler gradient across the aortic valve on admission was 36 mm Hg. The reduced function and echogenicity of the left ventricle were confirmed. There was a large ductus arteriosus. The remnants of the balloon used for the first procedure were seen in the left ventricular outflow tract close to the septal wall. Balloon dilatation with a Schneider-Shiley catheter passed retrogradely from the femoral artery was successful when he was 18 hours old. An aortogram showed mild distal aortic arch hypoplasia but seemed to exclude aortic coarctation. There was no increase in Doppler estimated velocity around the aortic arch.

The infant required continuous ventilation and circulatory support. Left ventricular function initially seemed to improve but by day 10 it was dyskinetic. Renal failure developed and was treated by peritoneal dialysis. By day 27, however, there was no recovery of renal function and the neonate showed impaired hepatic and left ventricular function. On Doppler examination there was no gradient across the aortic valve or around the aortic arch at this time and the duct had closed. After conferring with the parents, intensive care was stopped on day 28 and the neonate died.

A postmortem examination showed that the left ventricular wall was thickened and lined with fibroelastosis. The remnants of the original balloon catheter and guide wire lay in the left ventricular outflow tract but were firmly anchored in the myocardium. They were not causing an obstruction. The aortic valve was dysplastic though the cusps were cleanly split along the commissures. The diameter of the aortic root at the origin was 8 mm, with a maximum diameter of 11 mm in the ascending aorta. The aortic arch narrowed to 5 mm with the suggestion of a small, distal, discrete coarctation shelf when the arch was opened.

Discussion

Aortic valve disease can be diagnosed with accuracy by echocardiography before birth. The diagnostic features include a poorly contracting left ventricle, aortic valve thickening and restriction, a varying degree of left ventricular hypertrophy and echogenicity, and abnormal Doppler flow characteristics in the left heart. There may be little or no detectable flow into or out of the left side of the heart. The atrial septum is often closed at the initial examination, or closes as gestation advances, as shown in one of our patients.

In our prenatal series of 12 continuing pregnancies some cases did not survive until delivery and a further group did not live to reach either the catheter laboratory or surgery. Those who survived to undergo relief of aortic obstruction all subsequently died of endocardial fibroelastosis or left ventricular hypoplasia. In the face of this mortality we considered prenatal treatment.

The technique of transuterine cardiac puncture for fetal blood sampling or fetal transfusion is well established in specialised obstetric practice. During the procedures all the drugs normally necessary for resuscitation were available in doses appropriate to the fetal size. The balloon catheters used were a modification of those used in postnatal life and the procedure for positioning the guide wire and balloon within the valve was similar to that practised in children. Thus in the prenatal procedure we described we combined two established techniques and brought together the expertise of the two specialties.

It is important to consider the possible hazards to the mother and the fetus and to weigh them against the potential benefit of the procedure. Sterile techniques were used for insertion of needles and both mothers were given prophylactic antibiotics before and for 24 hours after the procedure. Maternal discomfort can be minimised by premedication and local anaesthetic at the site of needle puncture. It is possible that premature labour may be precipitated and this would require active treatment. There seems to be little associated tissue damage to the fetus. Haemorrhage from the puncture site may have caused the intrapleural collections found at necropsy in the first case though there was no intrapericardial blood. The fetal position of case 1 necessitated crossing the lung fields with the needle whereas the position of case 2 allowed a direct apical puncture and no intrapleural fluid was seen on ultrasound in the days after the procedure. In case 1, the needle itself apparently tore the aortic valve but this could be an intended first step when the guide wire fails to cross the aortic valve. In the second case, there was no evidence of a needle puncture site in the newborn at delivery one week after the interventional procedure nor was intracardiac trauma found at necropsy. The detachment of part of the balloon and its impaction in the ventricular wall in the second case was a technical error but one which may be avoided in the future by improvements in the design of the balloon catheters and needles.

It may be that patients with aortic stenosis who are suitable for this procedure require to be carefully selected. For example, where there is already established severe endocardial fibroelastosis or where the left ventricle is failing to produce an increased velocity of flow across the stenotic valve, ventricular damage may already be irreversible. Once the atrial septum is closed, relief of left ventricular obstruction alone may not be sufficient to maintain left ventricular growth. Where the conditions seem favourable for balloon dilatation of the aortic valve, it may also be necessary to dilate the mitral valve because there is often considerable inflow obstruction associated with aortic valve disease.

In summary, case 1 proved that delivery of the balloon to the left ventricle is possible in utero and case 2 that balloon dilatation of the fetal aortic valve is technically possible. Further experience with the technique will clarify which patients will benefit most from this form of treatment. Though the place of this form of treatment in the varying options for management of this condition has yet to be established, this preliminary step to prenatal treatment seems promising.

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Non-invasive assessment of perioperative myocardial cell damage by circulating cardiac troponin T

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Abstract

Troponin T is a unique cardiac antigen which is continuously released from infarcting myocardium. Its cardiospecificity as a marker protein might be particularly useful in assessing myocardial cell damage in patients undergoing cardiac surgery. Therefore, circulating troponin T was measured in serial blood samples from 56 patients undergoing cardiac surgery and in two control groups — 22 patients undergoing minor orthopaedic surgery and 12 patients undergoing lung surgery by median sternotomy. In both control groups no troponin T could be detected, whereas activities of creatine kinase were raised in all 12 lung surgery controls and activities of the MB isoenzyme were raised in five of the 12 patients in the lung surgery group and in four of the 22 patients in the orthopaedic surgery group, respectively. All the patients undergoing coronary artery bypass grafting (n = 47) and cardiac surgery for other reasons (n = 9) had detectable concentrations of troponin T. Five patients had perioperative myocardial infarction detected as new Q waves and R wave reductions. In these five patients troponin T release persisted and serum concentrations (5·5–23 μg/l) reached a peak on the fourth postoperative day. In the 51 patients without perioperative myocardial infarction serum concentrations and the release kinetics of troponin T depended on the duration of cardiac arrest. In patients in whom aortic cross clamping was short troponin T increased slightly on the first postoperative days; in patients with longer periods of aortic cross clamping troponin T concentrations were higher and remained so beyond the fifth postoperative day. In patients with non-specific changes on the electrocardiogram troponin T concentrations were significantly higher on days 1 and 4 after operation than in patients with normal postoperative electrocardiograms (11·2 (5) and 4·5 (2·6) *v* 8·2 (3·4) and 2·9 (1·6) μg/l).

Serum concentrations of troponin T showed some myocardial cell damage in every patient undergoing cardiac surgery. The persistent increases that were more common in patients with longer periods of cardiac arrest must have been caused by damage to the contractile apparatus. These results suggest that perioperative myocardial cell necrosis may be more common than indicated by changes of the QRS complex on the electrocardiogram.

Measurements of serum creatine kinase (EC 2.7.3.2) and lactate dehydrogenase (EC 1.1.1.27) activity and changes on the electrocardiogram are reliable indicators of acute myocardial infarction if there is no major damage to skeletal muscle. In patients undergoing cardiac surgery the value of these diagnostic methods is limited by enzyme release from non-cardiac tissues and non-specific changes (for example, ST segment and T wave) on the electrocardiogram.[1 2] Consequently, only major perioperative acute myocardial infarctions can be confirmed by these diagnostic methods.[3 4]

The specificity of serological testing for perioperative acute myocardial infarction can be improved by measuring the MB isoform of creatine kinase, but even creatine kinase MB is not a cardiospecific molecule[5–7] and some of the circulating creatine kinase MB, which is consistently found in patients undergoing cardiac surgery,[8 9] might well originate from non-cardiac tissues. Limited specificity hampers the assessment of the effectiveness of various cardioprotective measures.

Different protein isoforms in muscles can be identified by immunoassay.[10–12] Proteins derived from the contractile apparatus are released in patients with acute myocardial infarction and in some patients with unstable angina.[13–17] Sensitive assays that detect minor myocardial cell damage with high sensitivity and specificity would be especially useful in patients with concomitant damage to the skeletal muscle which is inevitable during cardiac surgery. We have measured circulating cardiac troponin T in patients undergoing cardiac surgery.

Patients and methods

PATIENTS

The first control group consisted of 22 patients with fractures of forearm, hand, shank, and foot admitted during a two week interval to an orthopaedic surgery ward (table). Skeletal muscle damage in this group was minor and resembled that in patients undergoing median

Clinical characteristics (mean (SD)) of the study groups

			Sex		Duration (min) of:		
Study group	*No*	*Age (yr)*	*M*	*F*	*Operation*	*Extracorporeal perfusion*	*Cross clamping*
Orthopaedic surgery	22	47 (18)	13	9	29 (21)	—	—
Thoracic non-cardiac	12	46 (17)	12	0	135 (54)	—	—
Cardiac surgery (coronary)	47	59 (8)	37	10	190 (42)	83 (40)	55 (27)
Cardiac surgery (non-coronary)	9	44 (17)	5	4	158 (42)	88 (34)	65 (25)

sternotomy. In this group of otherwise healthy patients we took blood samples on two consecutive days after operation.

The second control group consisted of 12 men undergoing median sternotomy for resection of mediastinal tumour or of solitary pulmonary metastasis (table). In three patients additional pericardectomy had to be performed; this was accomplished without major trauma to the heart. There was no evidence of important coronary artery disease in these patients as assessed by history, electrocardiogram, and preoperative exercise stress testing. After thoracic surgery there were no signs of myocardial ischaemia on the 12 lead electrocardiogram immediately after and six hours after operation. In this group of patients 10 ml blood was taken before and two, 16, 40, 64, and 88 hours after thoracotomy.

The coronary artery bypass graft group consisted of 37 men and 10 women (mean age 59 years) (table). At the time of coronary angiography 30 patients (64%) complained of unstable angina; this was stabilised by medical treatment in 21 patients before operation. The remaining 17 (36%) patients had stable angina. Left ventricular function was normal in 24 (51%) patients, impaired in 16 (34%) patients, and poor in seven (15%) patients. Previous myocardial infarction was found in 26 (49%), diabetes in 15 (29%), and impaired renal function in nine (10%) of the 47 patients. Coronary angiography showed one vessel disease in three (6%) patients, two vessel disease in eight (17%) patients, and three vessel disease in 36 (77%) patients. A mean of three bypass grafts per patient was implanted. The internal mammary artery was used as the bypass vessel in 27 patients. The mean durations of operation, of extracorporeal perfusion, and of aortic cross clamping were 190, 83, and 55 minutes, respectively. Two patients needed postoperative intra-aortic balloon counterpulsation.

The patient group with cardiac surgery other than coronary artery bypass grafting consisted of two patients with patch closure of an atrial septal defect, six patients with aortic valve replacement, and one patient with mitral valve replacement. The mean age of the four women and five men was 46 years (table). The mean durations of cardiac surgery, of extracorporeal perfusion, and of aortic cross clamping were 158, 88, and 65 minutes, respectively. Cardioprotection was achieved by infusion of a mean of 1·6 l Bretschneider HTK cardioplegic solution (sodium chloride 15 mmol/l, potassium chloride 9 mmol/l, potassium ketoglutarate 1 mmol/l, magnesium chloride 4 mmol/l, histidine 198 mmol/l, tryptophan 2·0 mmol/l, mannitol 30 mmol/l, pH 7·1, osmolality = 310 mosmol/l),[18] at 4°C into the aortic root. The heart was cooled externally by 4°C sodium chloride solution, to a mean myocardial temperature of 10·5°C. The body temperature was kept at 26°C by systemic hypothermia. Left atrial venting of the heart was routinely performed.

All patients gave informed consent to the study after thorough explanation of the protocol. The investigation was approved by the ethics committee on human research.

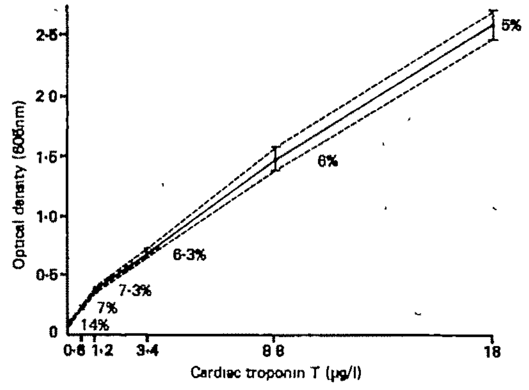
MEASUREMENTS OF CARDIAC MARKER PROTEINS

We collected 10 ml of blood before the operation; at the beginning and the end of extracorporeal perfusion; at the end of operation; 2, 8, 12, and 24 hours after surgery; and then once daily until the sixth postoperative day. The blood samples were stored at room temperature for 30 minutes to allow clotting. After centrifugation the serum was stored at −20°C until all blood samples had been collected.

Cardiac troponin T was measured by an enzyme immunoassay developed in cooperation with Boehringer Mannheim.[17] In this assay the troponin T molecule is bound by an affinity-purified cardiospecific sheep anti-troponin T antibody fraction immobilised on test tubes. Troponin T bound to the test tubes by these antibodies is then detected by the addition of a monoclonal anti-troponin T antibody labelled with horseradish peroxidase. This peroxidase labelled second antibody binds to the troponin T molecule on its specific epitope. The peroxidase activity adhering to the assay tubes after several steps of washing is assessed by colorimetric measurement of substrate conversion.

The troponin T measurements were performed in duplicate by a batch ELISA analyser (Enzymun Test System ES 22, Boehringer Mannheim). In this system 200 μl of the patient's serum sample was added to the test tubes; the addition of 1 ml peroxidase labelled monoclonal anti-troponin T antibody and all washing steps were performed semi-automatically. The test results were obtained in 90 minutes. The assay detected from 0·5 to 18 μg/l with inter-day coefficients of variation ranging from 5·0 to 7·0% (fig 1). The analytical sensitivity of this test was determined as the mean value + 3 SD of non-specific colour change in the test tubes containing 5% bovine serum albumin buffer solutions. The background colour change under these conditions was equivalent to 0·25 (0·11) μg/l of troponin T. The mean substrate conversion in 126 healthy volunteers and a pool of blood donors was equivalent to 0·18 (0·1) μg/l of troponin

Figure 1 Mean (1 SD) of all 10 standard curves of the cardiac troponin T test performed on different days during the study. The coefficients of variation are indicated as percentage values at each protein standard concentration.



T.[19] Thus in normal human serum no circulating troponin T was found at the sensitivity limit of this assay because non-specific binding and the imprecision of the test precluded a quantitative analysis of troponin T concentrations below 0·5 µg/l. In the present study the test result of sera below 0·5 µg/l was recorded as "not increased" and the results of the measurements were given.

Screening assays and immunoblot analysis showed that the affinity-purified antibodies only reacted with cardiac troponin T. However, because of non-specific absorption of purified skeletal troponin T to the assay tubes there was a 1–2% cross reactivity with troponin T extracted from mixed human skeletal muscle.

We measured total serum creatine kinase activity in a Chem 1 analyser (Technicon, Terrytown, USA) using the reagents provided by the manufacturer. We used an immunoinhibition assay for creatine kinase MB.[20] The upper limit of the normal range at 25°C was 75 IU/l for total creatine kinase and 10 IU/l for creatine kinase MB.

ELECTROCARDIOGRAM

A 12 lead electrocardiogram was obtained before operation; 2, 6, and 48 hours after operation; and then once on the seventh postoperative day. Diagnostic criteria for perioperative acute myocardial infarction were new Q waves of > 0·04 ms and reductions in the R wave of > 25% in at least two leads of the 12 lead electrocardiogram on day 7. Newly detected conduction defects and changes in the ST segment, T wave, or QRS complex not diagnostic for acute myocardial infarction were regarded as non-specific. The electrocardiogram was analysed by an experienced cardiologist (KWD) who was unaware of the serological test results.

STATISTICAL ANALYSIS

Linear regression analysis and analysis of variance was used throughout the study. Statistical significance was set at the 5% probability level. The table gives mean values and their standard deviation. The changes in the serum concentration of cardiac troponin T are shown as medians and interquartile ranges (25–75%).

Results

RELEASE OF MARKER PROTEIN IN THE STUDY GROUPS

Figure 2 shows the peak serum concentrations of troponin T and total creatine kinase activity in the 22 patients who had minor orthopaedic surgery, 12 patients who had lung surgery by median sternotomy, 51 patients with cardiac surgery, and five patients with cardiac surgery and perioperative acute myocardial infarction. Cardiac troponin T was undetectable in the patients in both control groups (median colour change of substrate solution corresponding to 0·18 µg/l and 0·21 µg/l troponin T). In patients who had cardiac surgery serum concentration of troponin T was at least twice the analytical sensitivity of the assay (median 5 µg/l, range 1·3–11 µg/l). The troponin T concentrations were significantly higher in the patients with electrocardiographic signs of perioperative acute myocardial infarction (median 11 µg/l, range 6–31 µg/l) than in the cardiac surgery group without acute myocardial infarction ($p < 0·01$).

We measured total serum creatine kinase activity to indicate the extent of skeletal muscle damage in the same group of patients. Total serum creatine kinase activity was increased in all but five patients in the control groups and in all 56 cardiac surgery patients. Peak serum creatine kinase activity was significantly higher in the patients with perioperative acute myocardial infarction (median 600 IU/l, range 370–1600 IU/l) than in the control groups and in the remaining patients who had cardiac surgery. Measurements of serum creatine kinase MB activity gave four and five false positive test results in the groups who had orthopaedic and lung surgery, respectively. Creatine kinase MB was increased in all but one patient in the cardiac surgery group (median 22

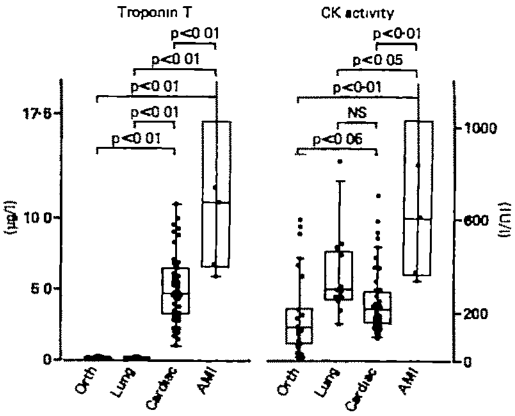


Figure 2 Peak concentrations of cardiac troponin T and peak serum creatine kinase activities in 22 patients who had minor orthopaedic operations, 12 patients who had lung surgery and median sternotomy, 51 patients who had cardiac surgery, and five patients who had cardiac surgery and perioperative acute myocardial infarction. The analytical sensitivity of the troponin T test and the upper limit of normal creatine kinase activity are 0 5 µg/l and 75 IU/l, respectively. AMI, cardiac surgery group with perioperative myocardial infarction; Cardiac, group that had cardiac surgery without perioperative myocardial infarction; Lung, lung surgery group (median sternotomy); Orth, orthopaedic surgery group.

IU/l, range 8–47 IU/l) and in all patients with perioperative acute myocardial infarction (median 70 IU/l, range 21–231 IU/l).

CHANGES IN THE SERUM CONCENTRATION OF TROPONIN T IN THE 56 PATIENTS IN THE CARDIAC SURGERY GROUP

Figure 3 shows the 51 patients who had cardiac surgery without perioperative acute myocardial infarction ranked according to their aortic cross clamp time. The three ranked groups show the effects of duration of cardiac arrest on the release kinetics of troponin T. Serum troponin T was increased immediately after surgery, peaked on the first postoperative day, and declined slowly thereafter. The serum concentration of troponin T, and the length of time it was increased, increased with the duration of aortic cross clamping.

In the five patients with perioperative acute myocardial infarction (figure 3, lower part) troponin T concentration remained high (up to 20 times the analytical sensitivity of the test) on day 5 after operation. Troponin T concentrations reached a peak (11 μg/l) (range 6–31 μg/l) on the first postoperative day and remained high with a second less well defined peak of 8·4 μg/l (range 5·5–23 μg/l) on the fourth day after operation.

EFFECTS OF DURATION OF CARDIAC ARREST ON RELEASE OF TROPONIN T

Both the peak troponin T concentration on days 1 and 4 and cumulative release of troponin T, assessed as area under the serum concentration curve, were associated with the duration of cardiac arrest ($p < 0{\cdot}001$, $p < 0{\cdot}01$, and $p < 0{\cdot}001$, respectively) (fig 4). The duration of extracorporeal perfusion ($p < 0{\cdot}005$, $p < 0{\cdot}01$, and $p < 0{\cdot}01$) and number of grafts implanted ($p < 0{\cdot}05$, NS, and $p < 0{\cdot}05$) were less strongly related to peak concentrations of troponin T on days 1 and 4 and total troponin T release after operation. Patients with preoperative symptoms of unstable or stable angina had similar perioperative concentrations of troponin T.

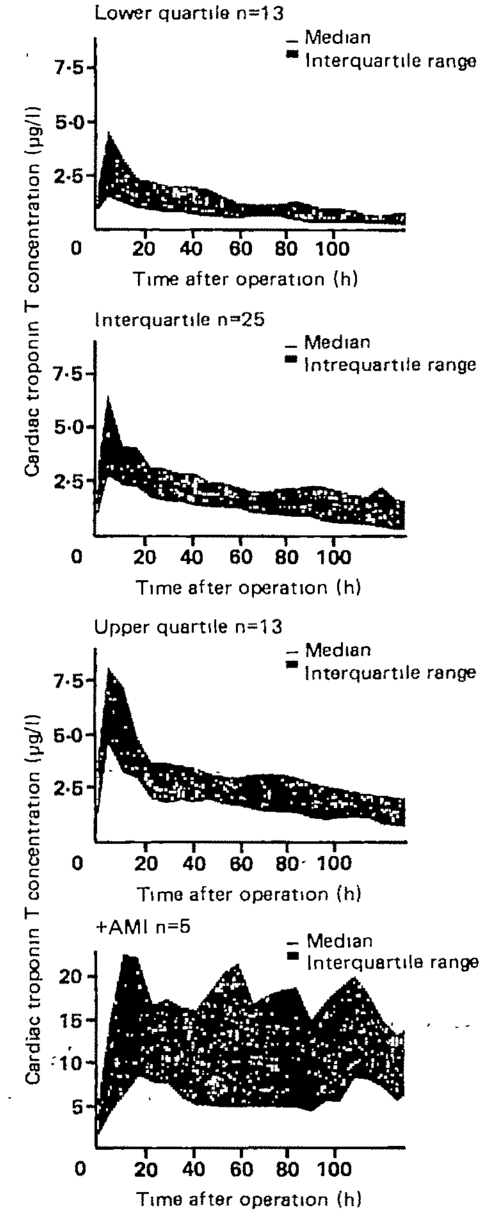


Figure 3 Median and interquartile range of changes in serum concentration of cardiac troponin T in patients who had cardiac surgery, showing its dependency on aortic cross clamping time. The patients are ranked according to their aortic cross clamping time: lower quartile (< 25%), interquartile, and upper quartile (> 75%). The changes in serum concentration in patients with cardiac surgery and perioperative myocardial infarction (+AMI) are also shown (note the different scale for troponin T values)

TROPONIN T RELEASE AND CHANGES ON THE ELECTROCARDIOGRAM

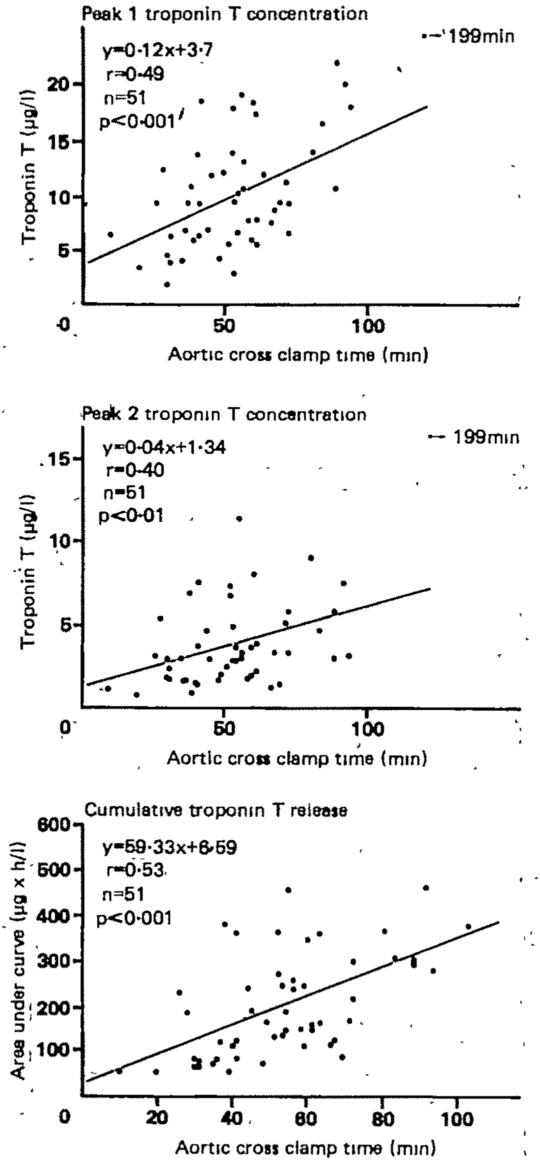
Figure 5 shows the peak serum concentrations of troponin T on days 1 and 4 and total troponin T release and the accompanying changes on the electrocardiogram in the 51 patients without perioperative acute myocardial infarction. Concentrations of troponin T tended to be higher in the patients with nonspecific changes on the electrocardiogram after operation.

Discussion

The detection and measurement of minor perioperative myocardial cell necrosis are indicators of the efficiency of cardioprotective measures and operative techniques. Diagnostic methods applied for the detection of acute myocardial infarction in a general hospital population cannot be used to identify minor myocardial cell damage in patients undergoing cardiovascular surgery. In patients undergoing cardiovascular surgery the electrocardiogram is only useful for detecting major acute myocardial infarction, and even in this subgroup of patients the electrocardiogram is of low sensitivity.[21] Electrocardiographic changes such as conduction disturbances or changes of the ST segment or T wave may be caused by minor or diffusely distributed ischaemic cell damage, but these changes are non-specific and cannot be used to evaluate the quality of cardioprotection.

Release of myocardial cell constituents is a common sequela of severe ischaemia, and detection of these cardiac molecules in circulation by quantitative assays indicates the extent of myocardial cell damage independently of its location and distribution within the heart. Yet

Figure 4 Dependency of troponin T peak values and cumulative release on aortic cross clamp time. Patients with perioperative acute myocardial infarction are excluded.



the marker proteins for perioperative cardiac muscle damage must be cardiospecific and should distinguish between reversible and irreversible cell damage. Some circulating creatine kinase MB activity found perioperatively[8,22–24] may originate from concomitant skeletal muscle damage. In addition, there is experimental evidence that cytosolic proteins such as creatine kinase MB, but not subcellularly compartmented molecules, can be released from anoxic but still viable myocytes.[25] Circulating creatine kinase MB does not always indicate irreversible myocardial cell necrosis.

Troponin T has a cardiospecific molecule with a distinctly different primary structure from its skeletal muscle isoform.[11] We used affinity purified polyclonal antibodies to distinguish between the cardiac and skeletal muscle isoforms of troponin T. The cross reactivity of 1–2% with troponin T extracted from skeletal muscle that we saw in the enzyme immunoassay resulted from non-specific absorption of purified skeletal troponin T on to the assay tubes. Because troponin T was not detectable in patients with skeletal muscle damage and creatine kinase activities up to 50 000 IU/l,[19] it may be that minor modifications of the skeletal troponin T molecule during the purification procedures increase the "stickiness" of this protein. In the present study as in a previous one,[19] there was no circulating troponin T in patients who had thoracic surgery only. This contrasts with the results for total creatine kinase and its MB isoform. Circulating cardiac troponin T, however, was found in all patients undergoing cardiac surgery on extracorporeal perfusion, indicating some myocardial cell damage in all of them.

After reperfusion in patients with acute myocardial infarction the release kinetics of serum troponin T resembled those of both structurally bound and cytosolic free proteins.[26,27] These release kinetics result from the intracellular compartmentalisation of troponin T, which is mostly bound to the contractile apparatus with only a small fraction in the cytosolic pool.[27] The increase in serum troponin T concentrations one day after surgery which we found in the present study in all patients with cardiac surgery may result from release of the cytosolic pool of troponin T. Two of the 56 patients who had a short period of cardiac arrest and no electrocardiographic changes had only this early troponin T release, which probably reflects minor and reversible ischaemic damage to the myocardial cell. In the remaining 49 patients undergoing cardiac surgery with longer periods of cardiac arrest and in the five patients with perioperative acute myocardial infarction there was a more long lasting increase (peak 2) in the serum concentrations of troponin T. Because the serum half life of troponin T is 120 minutes, the raised serum concentrations are likely to be the result of the continuing release of troponin T from the disintegrating contractile apparatus. This degradation of myofilaments most probably indicates irreversible cell damage, which may be diffusely distributed throughout the myocardium. Hence, in patients with a prolonged increase in serum troponin T the electrocardiogram showed non-specific changes rather than signs of myocardial infarction.

Diffuse myocardial cell necrosis after cardiac surgery was mainly encountered in patients with long lasting ischaemic cardiac arrest without cardioplegia. Despite excellent operative results these patients had severe left and even right ventricular pump failure. In our patients in whom cardioplegic solution and hypothermia were used for cardioprotection, cardiac ischaemia was well within experimentally determined periods of tolerance.[28] Yet, despite this good cardioprotection many patients showed evidence of persistent troponin T release. Thus under clinical conditions the tolerable ischaemic period may be shorter than forecast experimentally. This may be because the cardioplegic solution is unevenly distributed, or rapidly washed out from coronary circulation, or both.

In summary, the concentration of cardiac troponin T in serum can be used to identify and measure perioperative myocardial cell damage and may be useful in assessing the efficiency of

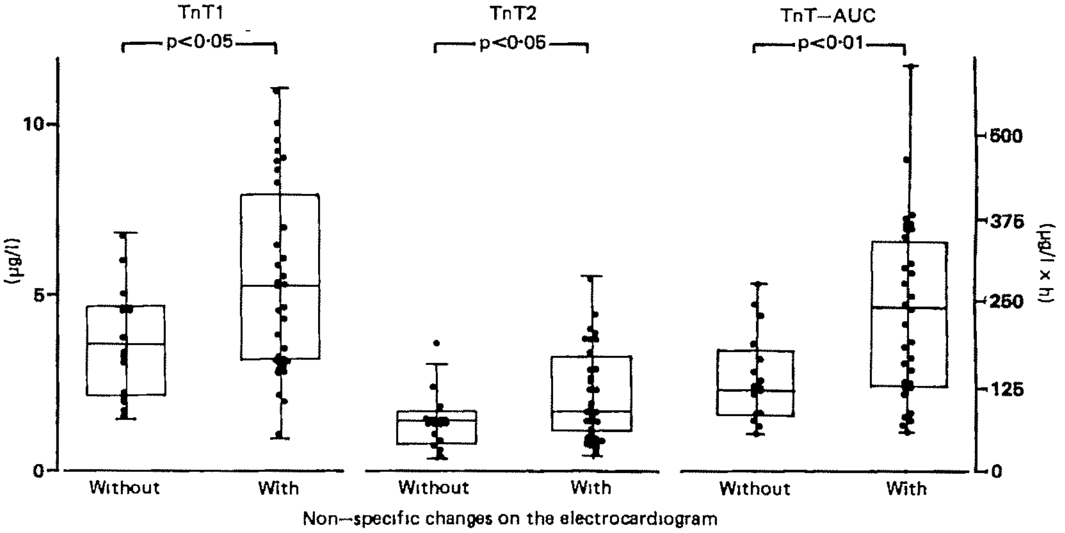


Figure 5 Changes on the electrocardiogram and in troponin T release in patients who had cardiac surgery. Non-specific changes on the electrocardiogram such as ST segment and T wave changes were more common in patients with increased early, late, and total troponin T release. Patients with perioperative acute myocardial infarction are excluded. TnT1, troponin T peak value on day 1 after operation; TnT2, troponin T peak value on day 4 after operation; TnT-AUC, cumulative release of troponin T calculated as area under troponin T serum curve.

cardioprotective measures. The persistent increase in troponin T found in some patients who had cardiac surgery suggests that cardioplegia cannot prevent ischaemic cell damage during long periods of cardiac arrest. Thus under clinical conditions the ischaemic period that can be tolerated by the myocardium may be shorter than studies on isolated hearts indicate.

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Characteristics of left ventricular filling in coronary artery disease and myocardial ischaemia after dipyridamole provocation

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Abstract

Doppler echocardiographic measurement of transmitral filling velocities seems to be a sensitive marker for resting left ventricular diastolic abnormalities in patients with coronary artery disease. The behaviour of these filling velocities during induced myocardial ischaemia, however, has not been fully studied. Left ventricular filling was assessed by pulsed Doppler ultrasound in 21 patients with angina pectoris and coronary artery disease and in five controls (patients with chest pain but without myocardial ischaemia). High dose dipyridamole infusion (0·9 mg/kg over 10 minutes) was used to provoke myocardial ischaemia, which was assessed by symptoms and electrocardiographic ST segment change. Doppler indices of diastolic filling were measured and the results expressed as percentage change from baseline values. Dipyridamole increased the heart rate and reduced systolic blood pressure equally in both groups. In the controls dipyridamole increased the peak filling velocities of both the early and atrial filling waves. In the 12 patients with coronary artery disease who did not develop evidence of myocardial ischaemia, the effect on left ventricular filling velocity resembled that in the controls though the time to peak change was delayed. Six of the nine patients with dipyridamole induced myocardial ischaemia had a significantly reduced maximum changes in early (+30% *v* +18%) and atrial (−0·2% *v* +33%) filling velocities compared with the controls. The remaining three patients had a decrease in early filling velocity (−20%) with an associated increase in atrial peak filling velocity (+21%).

Dipyridamole increased diastolic filling velocities in the controls. In patients with coronary artery disease there was a variable change in diastolic filling indices which may be attributed either to the degree of myocardial ischaemia or to the different haemodynamic changes occurring during myocardial ischaemia.

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Transmitral pulsed Doppler ultrasound confirmed resting abnormalities of diastolic function in patients with coronary artery disease.[1-3] These were a decrease in the peak velocity of the early filling wave together with an increase in peak velocity of the atrial filling wave; changes which in a simple form may be equated with a decrease in left ventricular compliance. This reversal of the normal filling pattern was also seen in those cardiac conditions in which there is evidence of hypertrophy or fibrosis of the left ventricle.[4-6] In patients with coronary artery disease this finding has been attributed to the presence of left ventricular fibrosis caused by infarction below the thresholds of clinical diagnosis or perhaps subsequent upon recurrent episodes of ischaemia.

During provoked myocardial ischaemia an increase in left ventricular diastolic pressure may lead to a decrease in the transmitral pressure gradient and would therefore be expected to decrease further the peak velocity of the early filling wave. Such changes have been shown in animal models[7 8] and also in humans,[9-11] when during angioplasty of the left anterior descending coronary artery early peak flow velocity fell and atrial velocity increased. In these reports ischaemia was induced by abrupt occlusion of coronary flow by the balloon procedure but it is not known whether these changes occur during demand provoked myocardial ischaemia. This in part is because of the technical difficulties of recording and analysing transmitral Doppler signals during exercise.

As an alternative to exercise dipyridamole can be used to provoke myocardial ischaemia. Dipyridamole is a potent coronary arteriolar vasodilator when it is infused intravenously and it causes myocardial ischaemia possibly by a mechanism of coronary steal.[12]

The aim of this study was first to examine left ventricular filling characteristics by transmitral pulsed Doppler ultrasound during infusion of dipyridamole in controls and in patients with coronary artery disease and secondly to observe the behaviour of left ventricular filling indices in those patients in whom myocardial ischaemia developed.

Patients and methods

CONTROLS

We studied five controls (mean age 45, range 30–63 years; three men and two women) who presented with chest pain atypical of myocardial ischaemia. In each the resting electrocardiogram was normal and the results of treadmill exercise testing by Bruce's standard protocol showed no ischaemic response.

Echocardiography with particular reference to left ventricular anatomy was normal. Each patient underwent coronary angiography and left ventriculography at the time of left heart catheterisation to confirm that left ventricular function and the epicardial coronary vessels were normal.

PATIENTS

We studied 21 patients (mean age 58, range 50–70 years; 13 men and eight women) who presented with chest pain typical of angina pectoris with ST segment depression and chest pain during treadmill exercise testing by Bruce's standard protocol. All patients had normal left ventricular systolic function on echocardiography with no global or regional wall motion abnormality and no left ventricular hypertrophy. Each patient underwent coronary arteriography and left ventriculography and had at least one major stenosis of a coronary vessel (>70% reduction in lumen diameter from one or more projections or >50% from two or more angiographic projections). All patients had angiographically confirmed normal left ventricular function and no evidence of mitral regurgitation or aortic valve disease. Table 1 shows the patient characteristics of both groups.

The controls were studied without medication. Patients in the study group who were taking β blockers and calcium antagonists were treated with sublingual glyceryl trinitrate instead of their normal medication for three days before the study. No drugs were taken on the study day. The study protocol was approved by the hospital ethics committee and written consent was obtained from all patients.

STUDY PROTOCOL

All patients were studied in the supine left lateral position by combined Doppler and cross sectional echocardiography with a 3·5 MHz transducer (General Electric Pass 11). Transmitral flow velocities were recorded by pulsed Doppler from the apical transducer position in a four chamber view with reference to the mitral inflow. From this position the Doppler sample volume was placed at the level of the mitral annulus and parallel to the mitral inflow. We kept the sample volume in a consistent position below the mitral valve apparatus. All recordings were performed during passive held expiration with simultaneous imaging of the left ventricle and lead II of the electrocardiogram.

Recordings of transmitral flow velocities were performed for five minutes to obtain baseline values. Dipyridamole was then infused via an antecubital vein at a dose of 0·6 mg/kg over four minutes followed by a dose of 0·3 mg/kg commencing at eight minutes for a further two minutes. Doppler recordings were taken for approximately 15 seconds every minute during and after the infusion for a total of 20 minutes. Aminophylline (50–250 mg) was given by intravenous injection at the end of the procedure or earlier if chest pain or ST segment depression occurred.

Throughout the 20 minute procedure, automated measurements of heart rate, blood pressure, and 12 lead electrocardiograms were taken every two minutes. In the controls during dipyridamole infusion the mean (1 SD) maximum heart rate increase was +27 (7)% and the maximum fall in systolic blood pressure was −10 (16)% compared with baseline values. In the patients with coronary artery disease the maximum heart rate increase was +18 (10)% and the maximum systolic blood pressure decrease was −14 (10)% during dipyridamole infusion compared with baseline values. Dif-

Table 1 Patient characteristics

Patient	*Age (yr)*	*Sex*	*CAD*	*Exercise test (time to ST depression (min))*
Controls				
1	63	M	None	N
2	30	M	None	N
3	50	M	None	N
4	41	M	None	N
5	43	F	None	N
Patients with coronary artery disease				
1	52	M	Cx	6
2	56	M	LAD + Cx	5
3	58	M	LAD	6
4	54	M	LAD	7
5	60	M	RCA + Cx	6
6	51	M	LAD	8
7	55	M	LAD	11
8	60	M	Cx	6
9	63	M	LAD	4
10	51	M	Cx	5
11	69	F	LAD	6
12	57	M	LAD	4
13	68	F	LAD	2
14	70	F	RCA	2
15	67	M	LAD + RCA + Cx	4
16	50	M	LAD + Cx	4
17	55	M	LAD + RCA	5
18	55	M	LAD + RCA	5
19	54	F	Cx	3
20	60	M	Cx	6
21	57	M	RCA + Cx	6

CAD, coronary artery disease, Cx, circumflex artery, LAD, left anterior descending artery; N, no ST depression on exercise testing; RCA, right coronary artery.

values. Differences between the two groups were not statistically significant.

ANALYSIS OF DATA

The peak flow velocities of both the early and atrial filling waves were measured by one observer using commercial software. The mean of three consecutive cardiac cycles was taken of the early and atrial filling indices for each of the one minute interval recordings. The mean velocities of the five minute preinfusion period were taken as baseline measurements. To allow direct comparison between individuals and between groups we used the percentage change of both early and atrial peak flow velocities from baseline measurements in the analysis of the data.

The 12 lead electrocardiograms were read by one observer and ST segment depression of greater than 1 mm in the chest or limb leads compared with baseline recordings was regarded as electrocardiographic evidence of myocardial ischaemia.

REPRODUCIBILITY OF MEASUREMENTS

To determine the reproducibility of the measurements of both peak early and atrial velocities, the original observer analysed 12 one minute interval recordings from 12 of the Doppler studies on two separate occasions. A linear correlation was calculated for the paired observations and the coefficient of variance was used to determine the intraobserver variation.

STATISTICAL ANALYSIS

All results were expressed as mean (1 SD). We used Student's two tailed *t* test (unpaired) to test the differences between groups; a p value $<0\cdot05$ was regarded as significant.

Results

CLINICAL RESPONSE

None of the controls (group 1) developed chest pain or electrocardiographic change during infusion of dipyridamole. Nor did 12 of the 21 patients with coronary artery disease (group 2). Nine of 21 patients (group 3) developed significant ST segment depression typical of myocardial ischaemia and, of these, six experienced their typical chest pain usually associated with effort. No patient had chest pain without electrocardiographic changes during dipyridamole infusion.

LEFT VENTRICULAR FILLING CHARACTERISTICS

The results of the Doppler study were analysed for left ventricular filling changes during infusion of dipyridamole. Figure 1A shows the effect of dipyridamole on left ventricular filling in group 1. In general there was an initial rapid increase in both peak early and atrial filling velocities with a maximum change in both velocities shortly after the first infusion of dipyridamole. The peak velocities then gradually decreased but did not reach baseline values at the end of the study period.

In most of the patients in group 2 the changes in both early and atrial filling velocities were similar to the changes in group 1. However, filling velocity changes reached a maximum after the second infusion of dipyridamole (Fig 1B). Patients in group 3 had two different left ventricular filling characteristics. Six of the nine patients (group 3A) showed a reduced maximum change in both early and atrial filling velocities compared with most of the patients in groups 1 and 2 (Fig 1C). The remaining three patients (group 3B) had a decrease in maximum change in early filling velocity accompanied by an increase in atrial filling velocity (Fig 1D).

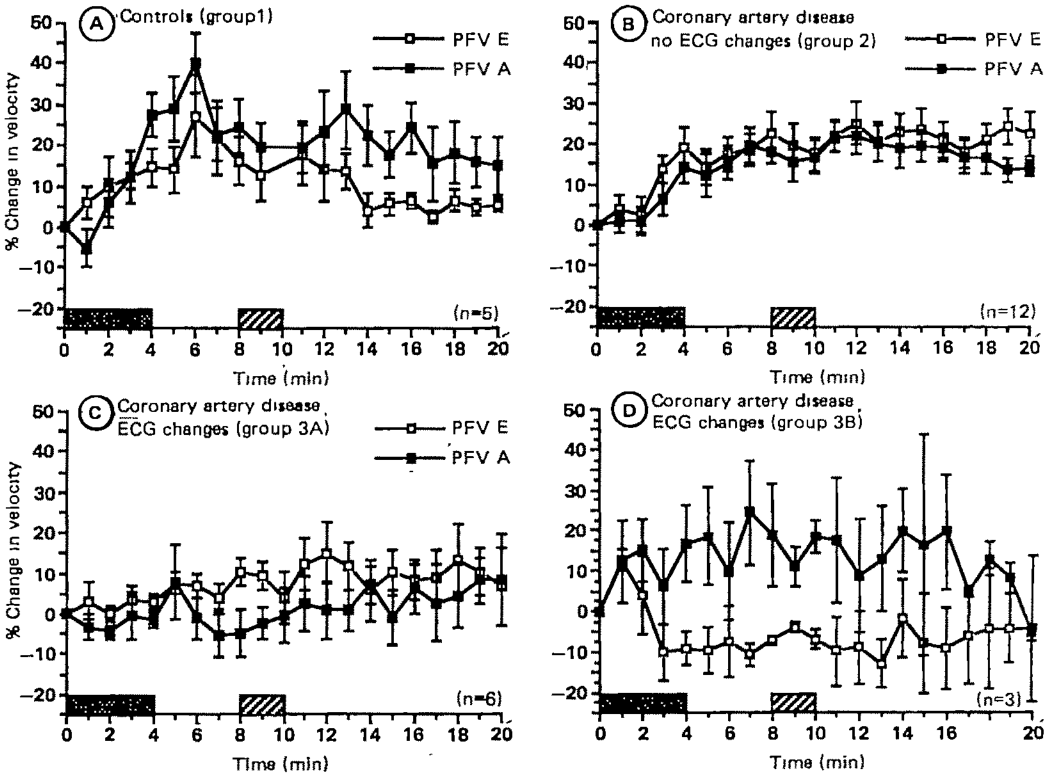

Figure 1 Mean percentage change and standard error of both early and atrial filling velocities during the study period. The stippled box is the first infusion of dipyridamole and the hatched box is the second infusion of dipyridamole. PFVA, peak flow velocity of atrial filling wave; PFVE, peak flow velocity of early filling wave.

Table 2 Maximum filling velocities

	% HR	% BP	E_b (cm/s)	E_m (cm/s)	% E	A_b (cm/s)	A_m (cm/s)	% A	E/A_b	E/A_m	% E/A
Group 1.											
1	19	39	31	48	55	56	72	30	0·56	0·67	18
2	28	6	70	88	25	45	79	75	1·56	1·11	41
3	24	0	45	51	15	67	80	20	0·67	0·64	−4
4	25	3	60	76	26	78	85	9	0·78	0·9	15
5	37	4	59	77	30	60	89	29	0·98	0·78	20
Group 2·											
1	40	17	72	91	27	63	82	29	1·13	1·0	−11
2	21	16	46	68	47	58	81	39	0·73	0·84	15
3	11	6	28	35	24	44	56	27	0·62	0·62	0
4	21	0	43	67	57	56	84	49	0·76	0·8	5
5	7	13	50	62	24	66	77	16	0·75	0·8	6
6	35	0	50	79	59	56	80	42	0·89	1·0	12
7	12	36	46	62	34	59	71	22	0·78	0·87	11
8	12	3	50	55	8	63	58	−17	0·81	0·95	17
9	15	0	38	59	54	49	59	21	0·78	1·0	28
10	17	19	58	69	20	72	75	3	0·8	0·93	16
11	25	11	37	59	62	77	98	27	0·47	0·6	28
12	32	10	62	78	26	59	79	34	1·04	0·98	−5
Group 3A											
1	19	22	45	50	11	37	33	−11	1·2	1·5	25
2	28	13	47	52	10	85	81	−4	0·56	0·64	14
3	21	36	47	64	37	54	66	23	0·87	0·97	11
4	2	24	45	58	29	88	82	−8	0·55	0·66	20
5	18	12	41	47	9	74	73	−1	0·56	0·65	16
6	11	24	51	56	9	62	62	0	0·83	0·93	12
Group 3B											
1	5	6	78	58	−25	52	54	4	1·52	1·08	−29
2	21	12	79	63	−20	31	36	16	2·55	1·74	−32
3	24	13	92	79	−14	36	52	44	2·54	1·52	−40

% HR, maximum percentage increase in heart rate, % BP, maximum percentage decrease in systolic blood pressure; E_b, baseline early filling velocity; A_b, baseline atrial filling velocity; E/A_b, baseline ratio of early and atrial filling velocities, E_m, maximum early filling velocity, A_m, maximum atrial filling velocity, E/A_m, maximum ratio of early and atrial filling velocities; % E, % A, % E/A, percentage change from baseline

INTRAOBSERVER VARIABILITY OF DOPPLER MEASUREMENTS

There was a strong linear correlation for repeated measurements of peak early and filling velocities (r^2 = 0·99 and r^2 = 0·98 respectively). The intraobserver variation for repeated measurements gave a coefficient of variance of 1·2% for peak early velocity and 1·4% for peak atrial velocity.

DOPPLER ANALYSIS AND CHANGES DURING MYOCARDIAL ISCHAEMIA

Table 2 shows the individual values for the haemodynamic changes during dipyridamole infusion and the early and atrial filling velocities and the E/A ratio at baseline and when the maximum early filling velocity was achieved in the study population.

The percentage change in early filling velocity in group 1 and group 2 patients (30·2 (15) and 36·8 (18) respectively) was significantly higher than in group 3A patients (18·5 (12); $p < 0·05$) and all these values were significantly different from the value in group 3B (−19·7 (5·5); $p < 0·01$). The percentage increase in atrial filling was similar in group 1, group 2, and group 3B patients (32·6 (25), 25·2 (15·9), and 21·3 (20·5)) and all were higher than in the group 3A patients (−0·2 (12·1); $p < 0·05$). The percentage change in E/A ratio in group 3B (−33·3 (5·7) was significantly lower than in group 1, group 2, and group 3A patients (18 (16), 10·2 (11·9), and 16·3 (5·3); $p < 0·01$) (fig 2).

Discussion

Left ventricular filling is a complex process that is governed by several interdependent variables. Theoretically it is regulated by the atrioventricular pressure difference generated by the elastic recoil of the left ventricle in diastole. The use of transmitral Doppler ultrasound to measure peak filling velocities, which are directly proportional to the atrioventricular difference, therefore allows non-invasive assessment of left ventricular filling.[13] The atrioventricular pressure difference, however, is influenced by left atrial pressure, rate of relaxation, left ventricular end systolic volume, and left ventricular and left atrial compliance[14-16] and therefore its usefulness as an index of diastolic function is thus dependent on the interpretation of these factors.

We studied the effects of dipyridamole infusion on left ventricular filling in controls and patients with coronary artery disease. Dipyridamole is known significantly to increase coronary blood flow and to provoke myocardial ischaemia mainly by a mechanism of coronary steal but also by slightly increasing myocardial oxygen consumption.[12] In the controls (group 1) the increased coronary flow induced by dipyridamole increased both early and atrial filling velocities. The concept that increased left ventricular filling velocities correlate to an increase in coronary flow accords with previous studies that showed similar favourable changes when coronary flow was improved to normal values by either aortocoronary artery bypass grafts[17] or successful coronary angioplasty.[18]

The increase in early filling velocities consequent upon increased coronary flow in the controls can be explained by the haemodynamic events that take place during dipyridamole infusion. Picano *et al* showed that

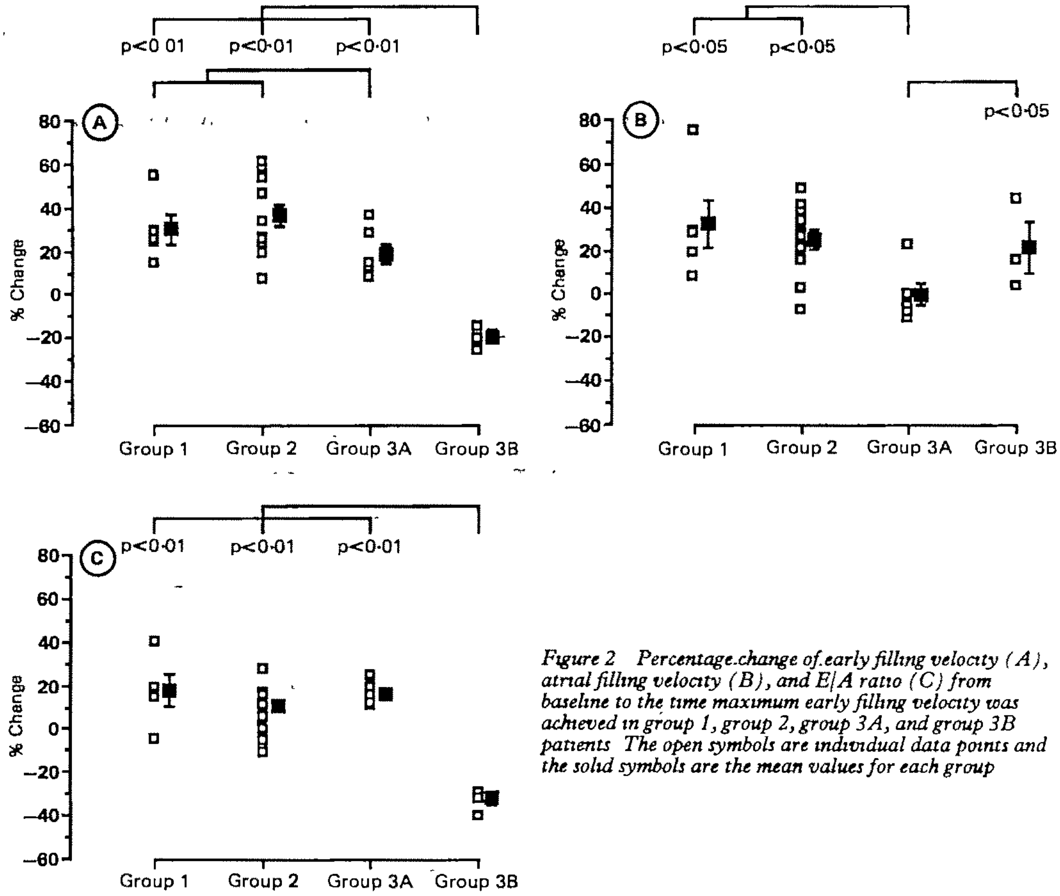

Figure 2 Percentage change of early filling velocity (A), atrial filling velocity (B), and E/A ratio (C) from baseline to the time maximum early filling velocity was achieved in group 1, group 2, group 3A, and group 3B patients The open symbols are individual data points and the solid symbols are the mean values for each group

during dipyridamole infusion both left ventricular contractility (positive dP/dt) and left ventricular relaxation (negative dP/dt) are increased whereas right ventricular pressures remain the same.[19] The overall effect is that left ventricular relaxation is faster and more complete; this enhances the atrioventricular pressure difference and consequently increases the early peak filling velocity.

In patients with coronary artery disease the left ventricular filling response fell into three broadly based categories. These categories represented a continuum from a normal response to a severe disturbance of left ventricular filling. The first resembled that in the controls and occurred in patients who did not develop electrocardiographic changes of myocardial ischaemia (group 2). In these patients there was a large increase in both early and atrial filling velocities. The second response occurred in six of the nine patients (group 3A) with dipyridamole provoked myocardial ischaemia. In this group most of the patients had a reduced but still positive change in maximum early filling velocity compared with the controls. This finding might suggest that these patients initially increased their coronary blood flow and that after the onset of myocardial ischaemia a decrease in the atrioventricular pressure difference limited any further rise in the early peak flow velocity. This hypothesis is supported by earlier studies which showed that during myocardial ischaemia the rate of relaxation (tau) is prolonged and because this also affects the atrioventricular pressure difference, peak flow velocity falls.[20 21] The reduced atrial filling velocities in these patients may be due to a failure of the normal atrial compensatory mechanism to maintain stroke volume in the presence of a reduced early peak filling rate and therefore possibly a reflection of decreased left atrial or left ventricular compliance or both.

The third response was that observed in patients of group 3B, in whom the early filling velocity decreased despite a theoretical increase in coronary flow during dipyridamole infusion. These patients seem to represent a group who develop more pronounced myocardial ischaemia and have a similar response to that seen when coronary vessels are occluded during balloon angioplasty.[9]

In the study from Lattanzi and coworkers similar changes were seen in transmitral flow velocities in patients with coronary artery disease who developed regional wall motion abnormalities during infusion of dipyridamole.[22] However, using a lower dose of dipyridamole, Grayburn *et al* were unable to record any differences in left ventricular filling for patients with coronary artery disease despite the documentation of dipyridamole induced thallium defects.[23] This group, however, only obtained one measurement of the transmitral flow velocities at an arbitrary time after dipyridamole infusion.

Despite the significant differences in left ventricular filling velocities between patients who did develop myocardial ischaemia and those who did not, there was some overlap between these groups. This implies that in individual patients, changes in left ventricular filling velocities during dipyridamole infusion could not with certainty predict whether myocardial ischaemia had occurred. If an earlier and more sensitive marker of myocardial ischaemia such as echocardiographic assessment of regional wall motion[24 25] had been used, however, it is possible that myocardial ischaemia may have occurred in some of the patients in whom ST segment depression did not develop (patients 8 and 10, group 2, table 2) but who had similar left ventricular filling velocities to patients who did (group 3A).

LIMITATIONS OF THE STUDY

Though no significant difference was seen in the haemodynamic changes produced by the infusion of dipyridamole in the two study groups, there was considerable variation between the subgroups particularly with respect to the blood pressure response and this might account for the observed changes in left ventricular filling. The effects of an acute reduction in blood pressure on left ventricular filling in patients with coronary artery disease has not been studied but indirect evidence from several investigators showed that reducing blood pressure in hypertensive patients[26] or acutely increasing blood pressure in normal individuals[27] had no effect on Doppler indices of left ventricular filling.

Another limitation of the study was that further valuable information derived from both the early and atrial filling waveforms could not be accurately analysed because the increase in heart rate induced by dipyridamole caused the waveforms to merge. The flow velocity integral gives a reliable estimate of cardiac output[28] and would have given valuable information in our patients on whether total cardiac output or the relative proportions of early and late transmitral volume flow were altered by dipyridamole infusion. The deceleration time of the early filling wave is known to be increased in patients with coronary artery disease[29] and may have further increased during myocardial ischaemia. However, even with these limitations we obtained useful information from peak flow velocities of both early and atrial filling waves during dipyridamole infusion which could not be obtained during exercise because the heart rates required to provoke myocardial ischaemia would have precluded even the measurements of peak flow velocities.

In conclusion, our study showed that dipyridamole increased the left ventricular filling velocities in the controls. In those patients who developed myocardial ischaemia, two distinct responses were seen which may be attributed either to the degree of myocardial ischaemia or to different haemodynamic changes occurring during myocardial ischaemia.

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Operative survival and 40 year follow up of surgical repair of aortic coarctation

J J Bobby, J M Emami, R D T Farmer, C G H Newman

Abstract

***Objective*—To study early and late mortality after surgical correction of coarctation of the aorta.**

***Design*—Data on 223 patients operated on at the Westminster Hospital, London, between 1946 and 1981, were collected and updated by questionnaire.**

***Participants*—All 223 patients recorded as undergoing operation for aortic coarctation up to the end of 1981. Fifteen of 197 survivors were lost to follow up; most of them were patients from overseas.**

***Outcome and results*—The early mortality (within one month of operation) was 12% overall, 2·6% for elective surgery, and 0% for the 77 patients undergoing surgery since 1968. Survivors were followed up for a total of 3288 patient years; in 27 follow up lasted more than 30 years. In a few it reached 40 years. Twenty two patients died during this period, 18 from causes that could be attributed to coarctation or its repair. Mortality was highest more than 20 years after the operation.**

***Conclusion*—Repair increased life expectancy in patients with aortic coarctation. Late problems caused by persistent hypertension or recoarctation became apparent in long term survivors. The increased risk of late mortality associated with the duration of preoperative hypertension was not statistically significant. There were no deaths from cerebrovascular accidents. (In an earlier necropsy series cerebrovascular accidents accounted for 11·8% of deaths.) The incidence of deaths from aneurysms resembled that in the earlier necropsy series.**

Operations to correct coarctation of the aorta have been carried out since 1944.[1 2] The earliest correction in the United Kingdom was performed by Sir Clement Price Thomas at Westminster Hospital in London in 1946. We have assessed the survival of patients who had the operation at Westminster Hospital since 1946.

Patients and methods

Between 1946 and 1981 223 patients with coarctation of the aorta were operated on at Westminster Hospital. Details of these patients were extracted from their discharge summaries and operation notes and from necropsy reports where available. Those who survived the operation were followed up to assess their present condition. Some of these patients had been followed up for up to 40 years and so the series gives valuable information about long term mortality and morbidity in patients who have had surgical correction of congenital coarctation of the aorta.

Of the original 223 patients, 156 (70%) were male. Thirty one (14%) were less than one year old at operation, a further 39 (17%) were 1 to 5, and 85 (38%) were aged from 5 to 15. Of the remaining 68, 15 (7%) were over the age of 30; the oldest was 48. Hypertension was common; about half the patients had a preoperative systolic blood pressure of $\geqslant 160$ mm Hg. Forty patients had had a period of heart failure. Some patients had associated lesions—notably, 10 had a ventricular septal defect and 31 a ductus arteriosus of whom seven also had a ventricular septal defect. In most patients the coarctation was postductal, but in 14 patients the coarctation was described as preductal and in 23 as juxtaductal.

The most common surgical technique was resection of the coarctation with end-to-end anastomosis. No record of the use of a Dacron patch was found. The subclavian flap technique was increasingly used from 1974. Pulmonary artery banding was also carried out on eight patients presenting with complex lesions in infancy, and where there was a ductus this was ligated. Only two patients who had pulmonary banding as part of their treatment survived—one with established pulmonary vascular disease despite the band, and the other, who was treated for ventricular septal defect with double aortic arch and coarctation, was well when last seen (debanded with the ventricular septal defect closed) but with some evidence of recoarctation six years after operation. No neurological complications were seen.

The total follow up time was 3288 patient years. The length of follow up ranged from one month to 40 years, with 107 patients being followed up for over 15 years and 27 for more than 30 years.

Results

OPERATIVE SURVIVAL

For the purposes of this analysis the patients were divided into those who had an elective

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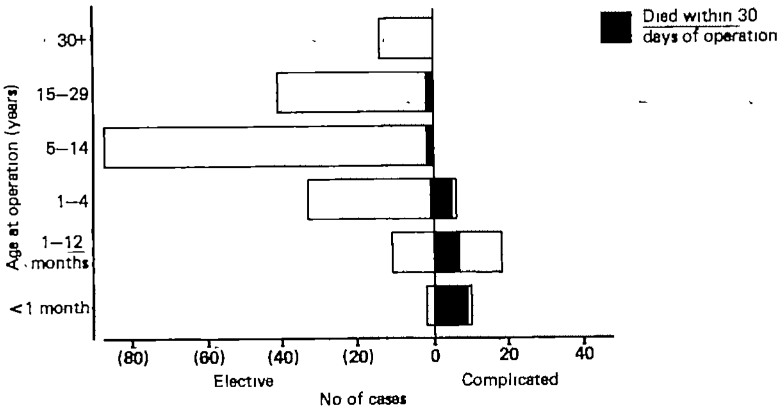

Figure 1 Deaths within 30 days of operation by age at operation.

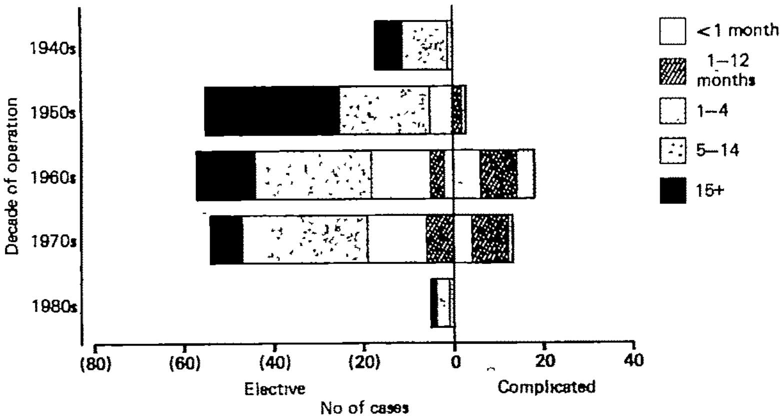

Figure 2 Age at operation by decade of operation.

Table 1 Ages at operation

Data	*Elective*	*Complicated*
Total	189	34
Average age at operation	12 yr	6 mnth
Range	1 mnth–48 yr	7 days–4 yr
Median age	8 yr 9 mnth	1 5 mnth
Died <1 day	3 (1 6%)	15 (40 5%)
Died <1 month	5 (2 6%)	21 (61 8%)

operation (189 patients) and those who required emergency or more immediate operation because of complicating factors including resistant heart failure, ductus arteriosus, or ventricular septal defect (34 patients). Patients were considered to have survived the operation and its immediate effects if they were alive 30 days from the date of operation (table 1).

Figure 1 shows the survival from operation by age at operation for the two categories. The mean age at operation was much less for the complicated cases; these operations were often emergencies performed on very young infants in severe heart failure, many of whom did not survive the operation. In contrast, over 97% of the patients who had elective operation were alive 30 days afterwards.

Nearly all (91%) of the operations were performed between the early 1950s and the late 1970s—all of the "complicated" cases were operated on before 1980. The patients who were operated on before the 1960s tended to be older (fig 2). There was no obvious trend in operative survival over the decades (table 2); however, between 1968 and the end of the study period there were no early postoperative deaths among the 7.7 patients who had elective operations. Of the five deaths among 112 patients who had elective operations up to 1968, three were operated on before 1950.

LONG TERM RESULTS OF REPAIR

Fifteen of the 197 patients known to have survived the operation were lost to follow up on discharge from hospital and were excluded from the analysis. Most of these were patients referred from abroad who returned to their homes after operation. Figure 3 shows all patients according to age at first operation. Twenty two of the 197 survivors died during the follow up. Five of these deaths were unrelated to coarctation or its repair. One patient died aged 5 from acute laryngotracheitis, three patients died from malignant neoplasms, and one drowned in a sailing accident; the last four all died after the age of 35 and had survived over 18 years since the repair of their coarctations.

The other 17 deaths could be attributed to coarctation, associated abnormalities, or the repair. All these patients had had end-to-end anastomoses. Table 3 summarises the age at operation, age at death, and underlying clinical cause of death in these patients. Five deaths were related to persistent coarctation; two of these patients died during further operations. Three other patients did not survive to the age of 20: one died aged 4 of septicaemia caused by acute bacterial endocarditis on a congenitally bicuspid valve (necropsy showed that the operation site was uninfected), one died aged 18 from congestive cardiac failure, and one at the age of 19 from an aneurysm related aortic-oesophageal fistula. There were five further deaths from aortic aneurysms. According to the reports, none of these was related to the operation site: one occurred in the arch of the aorta; two in the ascending aorta; and the exact site was not specified in the remaining two patients. There were four deaths from congestive cardiac failure. Ventricular fibrillation caused death in a patient who had already had a short previous attack in the absence of any apparent cause. There were no deaths from cerebrovascular accidents.

Table 2 Early mortality by year operation

	Elective		*Complicated*	
Year of operation	*Number*	*Number (%) died within 30 days*	*Number*	*Number (%) died within 30 days*
1946–49	17	3 (17 6)	0	0 (0)
1950–59	55	1 (1 8)	3	1 (33 3)
1960–69	56	1 (1 8)	18	13 (72 2)
1970–79	55	0 (0)	13	7 (53 8)
1980–81	6	0 (0)	0	0 (0)
Total	189	5 (2 6)	34	21 (61 7)

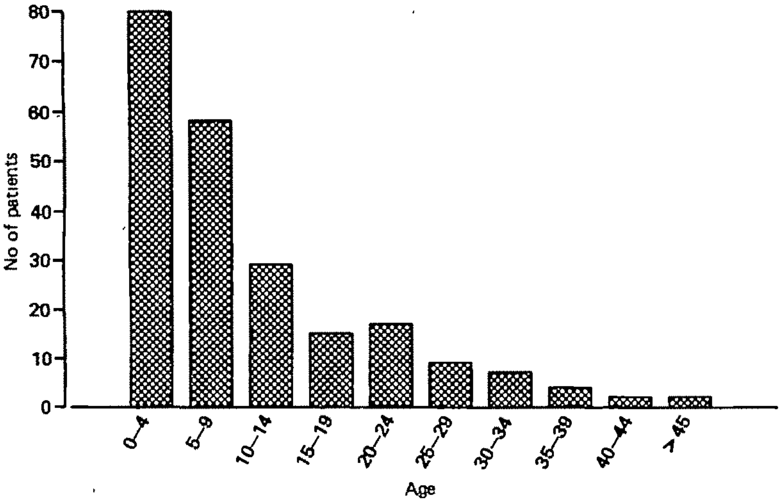

Figure 3 *Cases by age at first operation.*

The five patients who died from causes unrelated to their coarctation were considered as having left the study on their date of death. Figure 4 shows the survival and cumulative hazard functions: 3·8% died in the 10 years after the repair of their coarctation, 4·1% died between 10 and 20 years after the operation, and 9·2% died in the 10 years after that; thereafter mortality decreased. Only 27 people in the study were followed up for 30 years or more. It seems that even when general mortality was taken into account, the risk of dying from the effect of coarctation increased with the interval since operation. Only patients operated on before 1969 were followed up over 20 years, so the increase in mortality 20 years after operation might have been caused by problems with the early operative technique. But, because mortality by decade of operation showed no decline 10 and 15 years after operation, this seems unlikely.

FACTORS AFFECTING LONG TERM SURVIVAL

Age at operation

The patients were divided into three groups according to their age at operation—aged 4 years and under (56 cases), 5–14 years (76 cases), and ≥15 years (50 cases). Figure 5 shows plots of the Kaplan–Meier survival curves for each group. There was no statistically significant difference at the 0 05 probability level (when an approximation to Cox's F test was used) in long term survival between the groups, though a longer period of follow up might well indicate which age group fared the best. The best 20 year postoperative survival in our study was achieved by the 0–4

Table 3 *Information on 17 deaths related to cardiovascular disease*

	Age at operation (yr)	*Age at death (yr)*	*Causes of death*
1	6 wk	5	Died during operation to correct recoarctation of aorta
2	3 mth	11	Died during operation to correct recoarctation of aorta
3	4 mth	5	Septicaemia, acute bacterial endocarditis
4	1	22	Recurrent coarctation of aorta
5	5	19	Aortic-oesophageal fistula (presumed aneurysm—details unavailable)
6	5	30	Congestive cardiac failure
7	7	20	Ventricular fibrillation (previous episode of VF—no other abnormalities apparent before fatal recurrence)
8	10	33	Ruptured aortic aneurysm, persistent coarctation
9	11	22	Acute heart failure, aortic incompetence, persistent coarctation
10	11	18	Congestive cardiac failure
11	18	24	Ruptured aortic aneurysm
12	25	57	Aortic aneurysm, gross aortic incompetence
13	29	36	Congestive cardiac failure, aortic incompetence
14	30	41	Aortic aneurysm
15	30	40	Ruptured aortic aneurysm
16	31	53	Congestive cardiac failure, aortic stenosis, bacterial endocarditis
17	48	69	Congestive cardiac failure

All except patient 2 had end-to-end anastomosis The coarctation site was considered satisfactory or not mentioned in the necropsy report, unless otherwise stated.

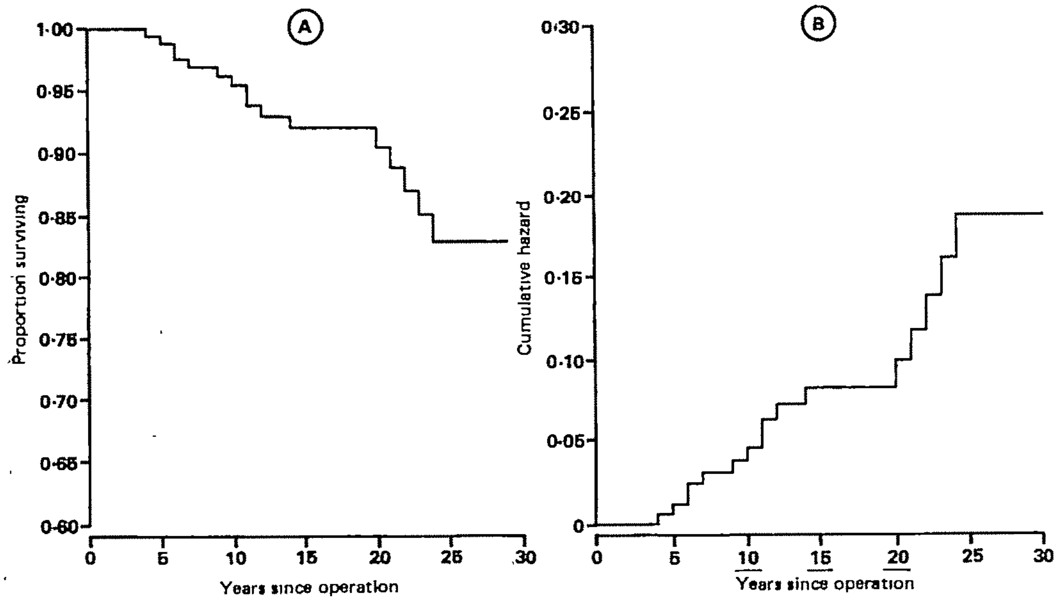

Figure 4 *(A) Long term survival in all cases, excluding perioperative deaths and (B) cumulative hazard in all cases, excluding perioperative deaths.*

age group. Thirty year survival was similar for all three age groups; because of the small number of patients (27) who have been followed up for 30 years this finding is not very reliable.

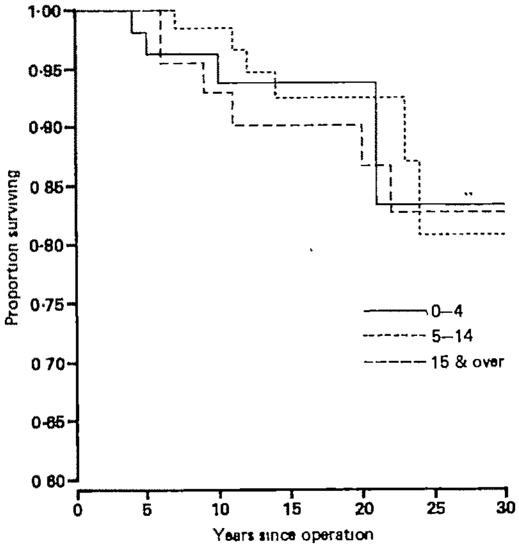

Figure 5 Long term survival by age at operation, excluding perioperative deaths

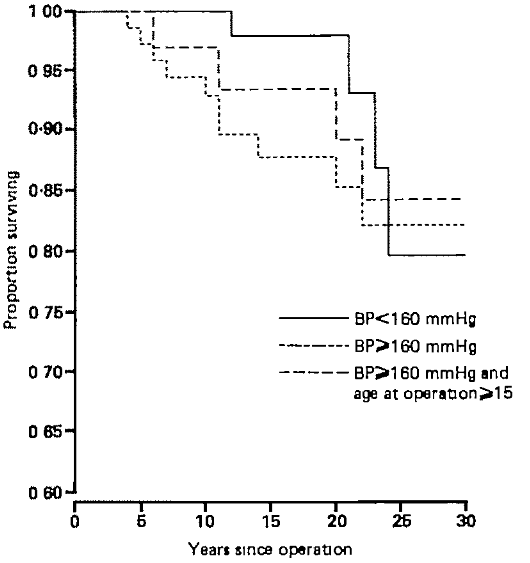

Figure 6 Long term survival according to blood pressure at operation and excluding perioperative deaths.

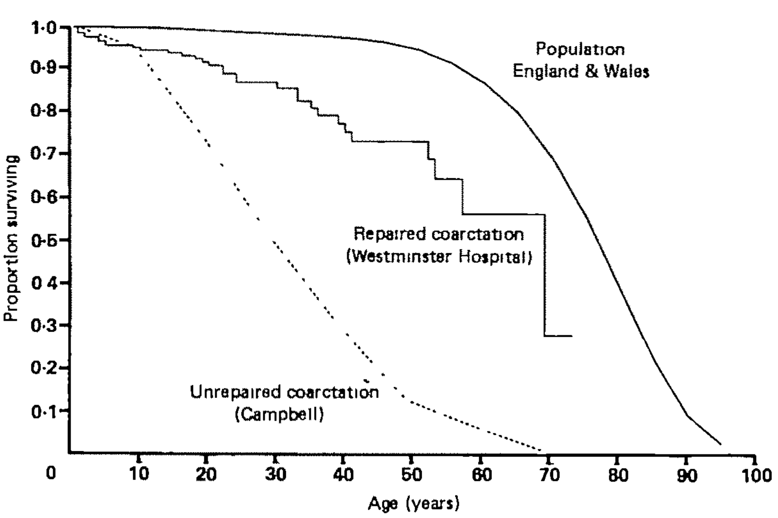

Figure 7 Comparative survival, excluding deaths in first year of life.

Hypertension

Figure 6 shows survival according to blood pressure at operation. Four of the 76 patients who had a systolic blood pressure of <160 mm Hg before the operation died in the follow up period compared with 10 of the 80 patients with a systolic blood pressure of $\geqslant 160$ mm Hg; however, this was not statistically significant at the 0·05 probability level. Figure 6 also shows the survival of patients who had a systolic blood pressure of $\geqslant 160$ mm Hg and were aged $\geqslant 15$ when they were operated on. Though they had had prolonged preoperative hypertension, their late mortality was no higher than in other groups, and their 30 year survival was better than those with a preoperative blood pressure of <160 mm Hg. For 26 patients we had no record of preoperative blood pressure.

OVERALL SURVIVAL

In 1970 Campbell estimated the mortality among patients who had coarctation of the aorta without surgical intervention.[1] Figure 7 shows the proportion surviving plotted against age for his set of patients and the results from the present study and normal mortality in the general population of England and Wales.[3] The results of our study are presented as an actuarial survival plot of the proportion surviving to reach each age, taking into account all deaths, whether perioperative or late unrelated to the coarctation. In all the plots, deaths under 1 year of age are excluded, because this is how Campbell calculated his figures. This plot showed that our patients survived longer than those with an unrepaired coarctation but not as long as the general population.

Discussion

Operative mortality for elective repair of coarctation of the aorta is low[4–6]—3% in our series of patients (0% since 1968). Without correction, the mean life expectancy of those with unoperated coarctation of the aorta is 35 years.[1] Correction of the coarctation has been shown by this and many other studies[5–10] to increase life expectancy.

Repair of aortic coarctation has been carried out since 1944.[2] As more patients enter their second, third, and fourth postoperative decades, problems associated with their coarctation and its repair are now becoming evident. Many studies have shown significant late mortality,[4 5 7 9 10] the rate being generally more than 10% when follow up exceeds 10 years. Some of our patients were followed up for 40 years and they included some of those who had the earliest operations for coarctation repair. The increase in mortality among these patients in the third decade after operation is worrying; Presbitero *et al* whose postoperative follow up ranged from 15 years to 30 years reported similar findings.[7] So far, very few patients have been followed up into their fourth postoperative decade (27 in this series) and it is difficult to give a longer term prognosis, but it seems likely that problems caused by recoarctation, vascular disease, and persistent hypertension will only increase with increasing age and time after operation.

Hypertension and vascular disease cause most of the morbidity and mortality associated with advancing age in patients with coarctation. Our results suggested an association between preoperative hypertension and an increased risk of later mortality. Others found that the younger the age at operation the greater the postoperative reduction in blood pressure[11] with late hypertension being more common when the operation was delayed until after the age of 20.[9] Maron *et al* suggested that the *duration* of preoperative hypertension is an important factor, with prolonged preoperative hypertension and operation after age 25 increasing the risk of premature cardiovascular death.[6] In our series 23 patients, with a preoperative blood pressure ⩾160 mm Hg systolic were operated on after age of 20 and survived the operation; all of them are still alive and have survived an average of over 20 years. These findings endorse Liberthson *et al*'s view that repair should not be denied on the basis of age or longstanding hypertension.[12]

The duration and severity of hypertension are also likely to be important factors in aneurysm formation remote from the repair site. Table 3 shows that in five of the six deaths related to aneurysms there had been exposure to hypertension and coarctation for more than 30 years in three, 25 years in one, and 18 years in two. Proximal distension, limited only by the degree and rate of development of collaterals, could be an equally damaging factor. Dissecting aneurysm of the ascending aorta caused late postoperative deaths in four patients and was detected in vivo in a further four of 343 survivors reported by Forfang *et al.*[13] In these patients surgical relief of coarctation occurred at age 9 (one) and at age 15–48 in the remainder. Aneurysm related to the repair patch is another hazard, discussed among others by Koller *et al.*[14] In the pre-surgical era, necropsy studies showed death from aneurysm rupture in 17·1% of 304 patients with coarctation reported by Abbott[15] and Reifenstein *et al.*[16] In our series, we found an even higher proportion of deaths related to aneurysm (27%), whereas so far there have been no deaths from cerebrovascular accidents, which accounted for 11·8% in the earlier necropsy series.[15 16] Relief of distension of the upper vascular segment and of hypertension after operation may be the reason; none the less aneurysm formation has persisted.

The desire to operate at an early age to reduce the risk of persistent hypertension and its associated problems must be balanced against the fact that residual and recurrent coarctation of the aorta are more common when the operation is undertaken in young patients,[5 10 11] though not necessarily with a worse outcome.[10] Of the five late deaths in our series in which persistent coarctation was a contributory cause, three occurred in patients who had their initial operation at the age of 1 or less.

It was hoped that subclavian flap arterioplasty[17] for the repair of coarctations would reduce recoarctation in infants. But this has not proved to be so. It seems that it is best to operate at the earliest age that gives the best results in the unit in which the operation is performed.

Doppler techniques,[18 19] angiography, or magnetic resonance imaging[20] can be used to show recoarctation of the aorta and other circulatory problems. Balloon dilatation may provide relief, and aneurysms can be monitored and operated on if indicated. These techniques mean that we can now do a more sensitive analysis than one based solely on mortality. It will then be possible to take prophylactic action to prevent further morbidity caused by recoarctation of the aorta, associated conditions, or problems associated with hypertension.

Additional work in progress shows that 80% of patients contacted claim to have experienced no symptoms or worsening in their quality of life after coarctation repair; yet many of the patients we re-examined 20+ years after operation were hypertensive despite absence of recoarctation. These data will be submitted for publication in due course.

We thank the Garfield Weston Trust for providing the funds to start this project; the Department of Child Health, Westminster Children's Hospital, for help with administration, Miss Clare Jenkins and Dr Kevin Walsh (former Garfield Weston Research fellow) who helped with much of the early work, and Miss Joan Smith and Mrs Dorothy Taylor for backup for the study We also thank Dr David Preston for his advice Most of the patients included in this study were operated on by Mr Charles Drew and his team. Mr Drew was appointed to the staff of Westminster Hospital in 1951 and undertook much pioneering work on congenital heart disease He died in May 1987

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Addendum

A further investigation into present state is underway. So far information is limited, but 68(80%) of the 85 survivors who were contacted because they had survived for 20 years or more consider themselves to be free of symptoms. Of the remaining 17 patients, 11 said they experienced some shortness of breath on exercise, such as running upstairs, five on more restricted exercise when walking upstairs, and only one when walking on the level.

So far, 22 patients have been reinvestigated 20–38 years after operation (mean 29) presently aged 21–51 years (mean 45) with age at operation being 1 month–45 years (mean 2 years). Blood systolic pressure readings (mm Hg) were as follows: > 160 in two; > 150 in four; > 140 in three. Diastolic pressures were > 90 mm Hg in eight.

Doppler assessment of the coarctation site showed velocities indicative of a gradient of between 0 and 30 mm Hg (mean 8·75 mm Hg). One patient had had a further operation for recoarctation, and two had had aortic valve replacement. So far no patients have had important aortic valve gradients.

Further follow up work is in progress, but it seems that recoarctation is not primarily responsible for most of the late hypertension.

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In vitro balloon dilatation of mitral valve stenosis: the importance of subvalvar involvement as a cause of mitral valve insufficiency

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Abstract
To investigate the mechanism that increases the orifice area of the mitral valve during balloon dilatation 43 surgically excised intact rheumatic mitral valves were studied. The main pathological features were (*a*) fibrosis of mitral valve leaflets and commissures (10 valves); (*b*) fibrosis with calcification of one commissure (eight anterolateral, seven posteromedial); (*c*) fibrosis with calcification of both commissures (seven valves); and (*d*) predominant involvement of the subvalvar apparatus (11 valves). The valves were assessed by photography and radiography before and after balloon dilatation (balloons up to 38 mm (bifoil 2 × 19 mm) and pressures up to 4 atmospheres). The valve was dilated in stages under direct visual control by balloons of increasing diameter. Splitting of the fused commissures was the most common mode of widening the orifice. However, the mitral valve leaflets were torn in two fibrotic valves and in six valves with extensive involvement of the subvalvar apparatus. In the fibrotic valves (group (*a*)) the tear originated near the valve perimeter, at the thinnest part of the remaining valve leaflet. In the valves with subvalvar involvement splitting started at the apex of spaces between the fused chordal columns and proceeded upward.

Where there is extensive involvement of the subvalvar apparatus in rheumatic mitral valve disease the risk of tearing of the valve leaflets by balloon dilatation is increased and this is likely to predispose to the development of acute valvar insufficiency.

The first report, by Inoue *et al*, of transvenous balloon dilatation of mitral valve stenosis in six patients, appeared in 1984.[1] The patients selected for this new technique did not have calcifications of the mitral valve apparatus or signs of mitral valve insufficiency. Because of good short term results and absence of major complications this procedure was soon used in patients with severe mitral valve stenosis, even those with calcifications and moderately severe mitral valve insufficiency.[2,3] At surgical operation Block *et al* showed that an earlier percutaneous balloon dilatation of the mitral valve had split the fused fibrotic and calcified commissures along their natural planes;[4] this effect was confirmed by cross sectional echocardiography.[5] In vitro analysis of the effects of balloon dilatation in surgically excised formalin fixed mitral valves also showed that splitting at the commissures, including those that were heavily calcified, was the prime mechanism.[6,7]

The initial success of commissurotomy of rheumatic mitral valve stenosis, in which the aim is also to open up fused commissures, was lower in calcified valves and valves with subvalvar involvement. Also restenosis appeared sooner and mitral valve insufficiency became a problem, either because it increased in severity or because it developed as a consequence of the commissurotomy.[8-11] Because balloon dilatation is basically a comparable procedure it is not surprising that these drawbacks to the technique have recently been recognised in calcified mitral valves and those with subvalvar involvement.[5,12-16]

In 40–50% of patients mitral valve insufficiency developed or increased after balloon dilatation; this effect was not foreseen with the echocardiographic grading systems used in earlier studies.[2,12,17] In most instances the mitral valve regurgitation so created is considered to be of little haemodynamic importance. None the less, acute severe mitral valve insufficiency can occasionally occur. The mitral valves of all of these patients showed extensive subvalvar disease and at surgery paracommissural tears of the valve leaflet were found.[13,18]

We found that several groups with rheumatic mitral valve disease can be distinguished on the basis of valve morphology. We investigated whether these groups showed any differences after dilatation of the excised mitral valves and, if so, whether any recommendations can be made about balloon dilatation in vivo.

Patients and methods

METHODS

We selected 43 mitral valves that were surgically excised because of rheumatic valve stenosis. All selected specimens had valves and subvalvar apparatus removed *en bloc*. The valves were fixed in 10% buffered formalin. The valves were classified on the basis of the main pathological feature: (*a*) a fibrotic group with fibrotic thickening of leaflets and fusion of commissures without calcifications; (*b*) a group with fibrosis and calcification of either the

Table Summary of results

		Site of tear			
Group	*No*	*ALC*	*PMC*	*Both*	*Leaflet*
Fibrosis	10	3	5 (1)	—	2
Calcification ALC	8	3	5 (2)	—	—
Calcification PMC	7	3 (1)	1	3 (3)	—
Calcification both commissures	7	1	4 (2)	2	—
Subvalvar	11	2	3 (1)	—	6 (1)
Total	43	12 (1)	18 (6)	5 (3)	8 (1)

ALC, anterolateral commissure; PMC, posteromedial commissure. Numbers in parentheses are completely disrupted valves.

anterolateral or the posteromedial commissure; (*c*) a group with calcifications within both fused commissures; (*d*) a group showing severe subvalvar disease (thickened, shortened, and fused chordae, leading to obliteration of the interchordal spaces) in addition to fibrosis and calcification. In patients in groups (*a*) to (*c*) the subvalvar apparatus was not involved or only slightly involved.

Photographs and radiographs were taken before and after dilatation. The degree of calcification was classified as slight, moderate, and severe.

Experimental design

The mitral valve was dilated with 8F 19 mm monofoil, 9F 19 mm trefoil (by placing a ligature around one balloon a circumference was obtained of 24 mm), 12F 15 mm bifoil, 9F 12 mm trefoil, and 12F 19 mm bifoil balloon catheters (Schneider). The catheters were attached to a manometer pressure gauge through a Y connection. The deflated balloon was introduced from the atrial side of the valve and advanced halfway down the valve.

After inflation of the smallest balloon, at a maximum pressure of 4 atmospheres, larger and larger balloons were used if no effects were seen. The results of this gradual increase in both the pressure and the balloon circumference were under direct visual control.

Results

The table summarises the results. In 35 out of 43 valves dilatation resulted in a tear, which opened up the fused commissures, both fibrotic and calcified. In 11 of the 43 excised valves the tear led to complete disruption. This event was spotted instantly and its mode of origin was visually identified. These valves, therefore, were not excluded from the evaluation. Ten of these 11 valves were completely disrupted by a continuation of a commissural tear. In the remaining valve there was extensive subvalvar involvement and the tear originated distally within the leaflet and extended upwards into the valve perimeter.

In valves with commissural calcifications no relation was seen between the site of the tear and the site of the calcification. Nor did the degree of calcification affect this outcome. The more severe the calcifications, however, the greater the chance of complete disruption. Seven of the 15 valves with severe calcifications were completely disrupted. Neither of the two moderately calcified valves was disrupted and only one of the remaining five slightly calcified valves. All the tears in the calcified valves were

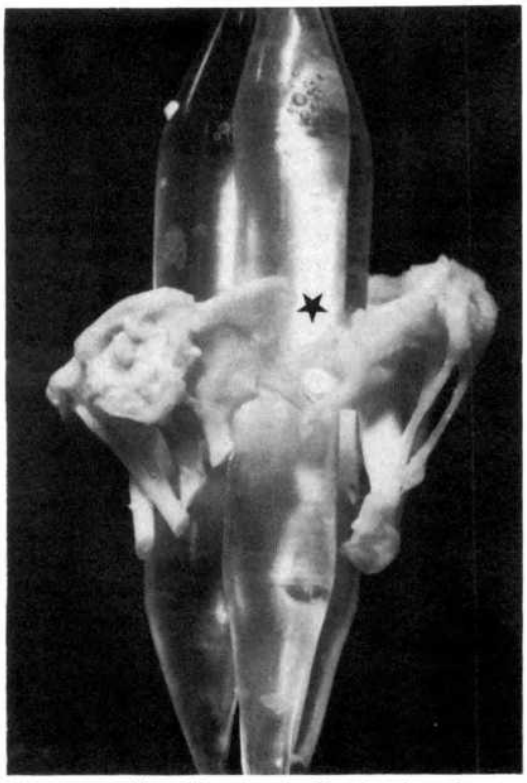

Figure 1 Balloon dilatation of a fibrotic valve. The tear started close to the valve perimeter (asterisk) through a previously fused commissure and proceeded downwards.

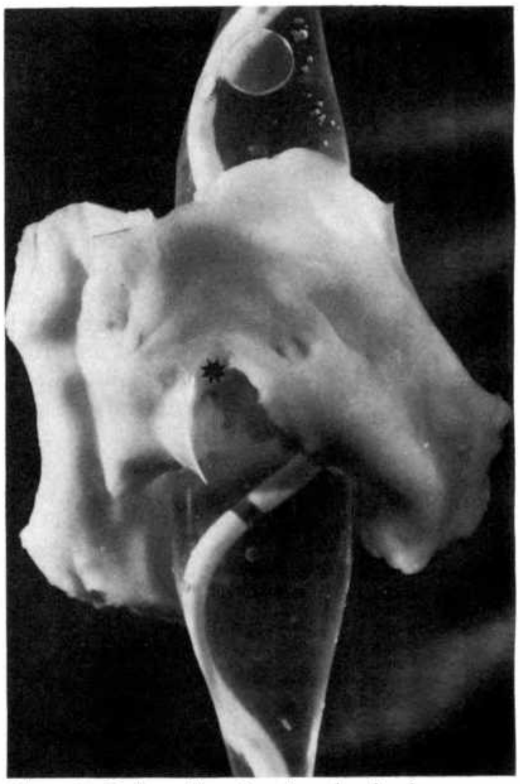

Figure 2 Balloon dilatation of a valve showing severe involvement of the subvalvar apparatus. The tear started at the apical side of the valve and proceeded upwards (asterisk) through the valve leaflet.

at commissural sites; none of the leaflets was torn.

In eight valves a leaflet was torn—two in valves with fibrosis without calcifications and six in valves with subvalvar involvement. In the fibrosed valves the tear always started to appear close to the valve perimeter at the thinnest part of the mural leaflet of the excised valve (fig 1) and in the group with subvalvar involvement it originated at the apex of spaces between the fused chordal columns and proceeded upward (fig 2).

In the group showing subvalvar involvement the aortic leaflet was torn in five cases and the mural leaflet in one. With one exception, all these unwanted tears occurred between fibrotic columns of fused chordae (fig 2). In one only, the laceration occurred in a severely calcified leaflet. All tears, moreover, originated on the ventricular side of the subvalvar apparatus and proceeded upwards towards the valve perimeter. In one of these complete disruption occurred. Since the calcifications in this group were diffusely dispersed throughout the valvar apparatus the relation, if any, between tears and calcific deposits could not be determined.

Discussion

Previous studies of in vitro balloon dilatation of the mitral valve showed that the mitral valve orifice increased by splitting of diseased commissures.[3 6 7] Our study confirmed these results. In the earlier studies, however, no lacerations were reported in the leaflets or the subvalvar apparatus but the type of disease affecting the mitral valve was not specified.

The morphology of the rheumatic mitral valve when there is severe involvement of the subvalvar apparatus suggested to us that the mechanism of balloon dilatation might be different and potentially dangerous. The valve leaflets are pulled down like a funnel so that the narrowed and deformed ostium is located well into the ventricle. The fibrosed leaflets contain columns of fused chordae. A balloon positioned and inflated in such an orifice will put pressure upon the walls of the ostium, which will dilate only when the unfortified parts tear. Because the chordae fuse almost randomly, tears can arise in the plane of a commissure or of one of the leaflets. The results of the present study accord with this theory. Of the 11 valves with a severely affected subvalvar apparatus, five showed a commissural tear, as expected, but in six a leaflet was torn. Moreover, each of these leaflet tears originated in the apex of spaces between the fused chordal columns of the affected subvalvar apparatus and extended upwards towards the valve perimeter.

Do the tears in two of the valve leaflets of the fibrotic group contradict our theory? In both instances we saw the tear starting close to the valve perimeter rather than in the apical parts. We believe that the lack of support at the annular level in these two valves was important. In both only a small rim of the valve leaflet had been excised at the site of the tear. Similarly, the outcome may have been affected by the fact that all valves had been fixed in formalin. This may have altered the mechanical properties of the tissues. Nevertheless, the results obtained in earlier in vitro experiments with formalin fixed valves have been shown to mirror those following balloon dilatation in life.[3 6 7]

Despite its limitations we believe that our study may have clinical relevance. Involvement of the subvalvar apparatus may increase the risk of laceration of the valve leaflets during balloon dilatation and this will lead to acute mitral valve regurgitation. In future clinical studies should be directed towards echocardiographic examination of the subvalvar apparatus.

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Fixed subaortic stenosis: anatomical spectrum and nature of progression

Jung Yun Choi, Ian D Sullivan

Abstract

Retrospective echocardiographic review identified 58 consecutive infants and children with fixed subaortic stenosis. Mean (SD) age at diagnosis was 4·8 (3·6) years (range two days to 14·7 years), and diagnosis occurred in infancy in eight. Associated cardiac abnormalities were present in 41 (71%) whereas fixed subaortic stenosis was an isolated lesion in 17 (29%). Four types of fixed subaortic stenosis were identified: short segment (47 (81%)), long segment (7 (12%)), posterior displacement of the infundibular septum with additional discrete narrowing of the left ventricular outflow tract (3 (5%)), and redundant tissue arising from the membranous septum (1 (2%)). Echocardiographic studies had been performed before the diagnosis of fixed subaortic stenosis in nine patients, all with associated abnormalities. These were performed in infancy in each and showed a "normal" left ventricular outflow tract in six and posterior deviation of the infundibular septum in three. In 16 patients serial echocardiographic studies had been performed after the diagnosis of fixed subaortic stenosis but before surgery of the left ventricular outflow tract. Rapid evolution of short segment to long segment narrowing was seen in one patient, and tethering of the aortic valve or mitral valve developed in a further four patients. Aortic valve or mitral valve involvement was not seen before the age of three years but was common thereafter (10/40 patients, 25%).

Fixed subaortic stenosis may be an "acquired" lesion with the potential for changes in form as well as progression in severity of left ventricular outflow tract obstruction.

Fixed subaortic stenosis can occur in isolation or in association with other structural heart defects but it is rarely diagnosed in infancy.[1–3] The subvalvar obstruction is usually a fibrous shelf or a long fibromuscular narrowing.[4 5] In contrast, when subaortic stenosis occurs in infancy it is more often the result of a malalignment ventricular septal defect with posterior deviation of the outlet septum into the left ventricular outflow tract, usually in association with coarctation or interruption of the aortic arch.[6]

Fixed subaortic stenosis progresses in severity[7] and may even present as an "acquired" condition.[5] The mechanism of progression is unknown. Further knowledge of the course would be a useful guide to optimal management, which is controversial.[7–9] Cross sectional echocardiography can define the nature of subaortic stenosis and can easily be repeated. Consequently, this study was performed to detail the echocardiographic findings of subaortic stenosis at different ages and to identify the nature of progression on serial studies.

Patients and methods

Echocardiographic and surgical records at the Hospital for Sick Children between April 1981 and December 1986 were reviewed. Fifty eight cases of subaortic stenosis with normal cardiac connections were diagnosed. The criterion for diagnosis was the demonstration of a localised subvalvar discrete ridge or long segment narrowing in the left ventricular outflow tract at echocardiographic examination. This was confirmed by inspection at operation or necropsy whenever possible. Long segment narrowing was diagnosed when the length of the obstruction in the left ventricular outflow tract was more than one third of the aortic valve diameter.[10] Patients with posterior deviation of the infundibular septum were excluded unless there was additional discrete narrowing in the left ventricular outflow tract. Similarly, patients with obstruction of the left ventricular outflow tract caused by hypertrophic cardiomyopathy were excluded. Mitral valve involvement was diagnosed when abnormal tissue was attached to the anterior mitral valve leaflet which tethered the anterior mitral leaflet during systole. Aortic valve involvement was diagnosed when abnormal tissue in the left ventricular outflow tract seemed to be tethered to the base of the aortic valve.

All available echocardiograms performed before or after the diagnosis of subvalvar aortic stenosis, but before surgical procedures on the left ventricular outflow tract, were reviewed to determine sequential changes. The echocardiograms had been recorded on U-matic or VHS video tape by an ADR SC-2000, ATL mark 5, ATL 600, Ultramark 4, or Ultramark 8 machine. During the course of the study, operation to the left ventricular outflow tract was undertaken in 30/58 (52%) patients, twice in three of them. Five patients died and a necropsy was performed in three of them.

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Anomalies associated with subaortic stenosis

Nature of subaortic stenosis	*n*	*Age at diagnosis range (median) (years)*	*Associated anomalies*											
			VSD	*Coa/IAA*	*BAV*	*SVMS ± MVS*	*LSVC*	*PDA*	*Inf PS*	*ASD*	*AVSD*	*APW*	*PVS*	*Distal Ao*
Short segment	49	0·1–14·7 (4·5)	19	13	6	5	7	6	1	1	2	1	1	0
Long segment	8	0·8–10·4 (4·0)	2	3	3	1	1	2	1	1	0	0	0	1
Membranous septum	1	2 days	0	0	0	0	1	0	0	0	0	0	0	0

APW, aortopulmonary window; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; Coa/IAA, coarctation or interruption of aortic arch; distal Ao, diffuse narrowing of distal aorta and iliac vessels; Inf PS, infundibular pulmonary stenosis; LSVC, persistent left superior vena cava; PDA, persistent ductus arteriosus; PVS, pulmonary valve stenosis, SVMS ± MVS; supravalvar mitral stenosis with or without mitral valve stenosis.

Results

ASSOCIATED ANOMALIES

The table shows the clinical characteristics and type of subvalvar aortic stenosis. Age at diagnosis ranged from two days to 14·7 years (mean 4·8 (3·6) years). There were 35 boys and 23 girls (sex ratio 1·5:1). Associated anomalies were present in 41 (71%) patients (table), whereas 17 (29%) had "isolated" subaortic stenosis. Common associated anomalies were ventricular septal defect (21 (36%)) and lesions resulting in obstruction to left heart flow such as coarctation or interruption of the aortic arch (16 (28%)), bicuspid aortic valve (nine (16%)), or supravalvar mitral stenosis (six (10%)). There was a persistent left superior vena cava draining to coronary sinus in 9 (16%) patients.

NATURE OF SUBAORTIC STENOSIS

Four types of subaortic stenosis were identified on echocardiographic review. There was short segment narrowing in 47 patients, long segment narrowing in seven patients, displacement of the infundibular septum with additional discrete obstruction in three, and abnormal tissue with a unique appearance in one patient. Figure 1 shows the echocardiographic findings at diagnosis of subaortic stenosis.

Short segment narrowing, apparently the result of a fibrous ridge or localised muscular bulging, was usually seen in long axis views. In almost all cases the parasternal long axis allowed better visualisation of the obstructing tissue in the left ventricular outflow tract than apical or subcostal views. Tilting the transducer slightly to either side of the true parasternal long axis plane showed whether the fibrous ridge was attached to the anterior leaflet of the mitral valve. The extent to which the ridge protruded into the left ventricular outflow tract varied according to the exact plane of the ultrasound beam in parasternal long axis views. The reason was apparent on careful parasternal short axis scans of the left ventricular outflow tract which showed the extent of the attachment of the subaortic ridge. This was sometimes confined to the left ventricular aspect of the infundibular septum but more often extended from the infundibular septum around the margins of the left ventricular outflow tract to the anterior leaflet of the mitral valve (fig 2). The ridge came into

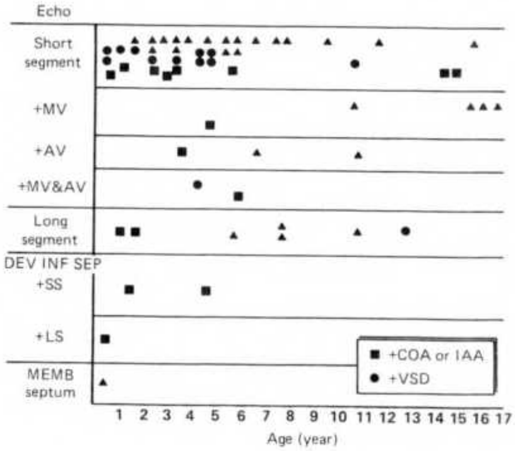

Figure 1 Echocardiographic findings at diagnosis of subaortic stenosis. Squares are patients with coarctation or interruption of the aortic arch with or without a ventricular septal defect. Circles are patients with a ventricular septal defect but without obstruction of the aortic arch. AV, aortic valve involvement; COA, coarctation; DEV INF SEP, deviation of the infundibular septum into the left ventricular outflow tract; IAA, interruption of the aortic arch; LS, long segment; MEMB, membranous; MV, mitral valve involvement; SS, short segment; VSD, ventricular septal defect.

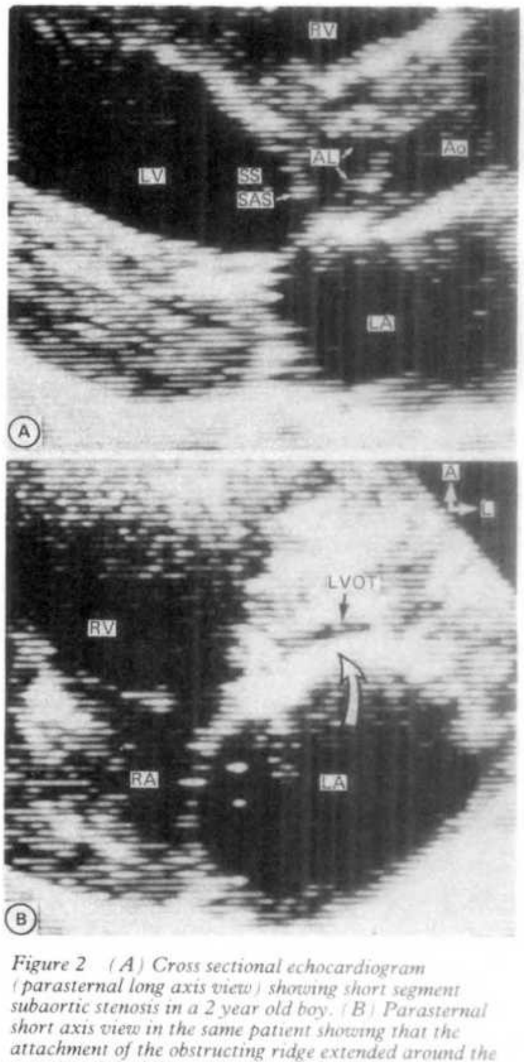

Figure 2 (A) Cross sectional echocardiogram (parasternal long axis view) showing short segment subaortic stenosis in a 2 year old boy. (B) Parasternal short axis view in the same patient showing that the attachment of the obstructing ridge extended around the margins of the left ventricular outflow tract to the anterior mitral valve leaflet so that the lumen of the outflow tract was reduced to a slit. The curved arrow indicates the base of the anterior mitral valve leaflet. A, anterior; AL, aortic valve leaflets; Ao, ascending aorta; L, left; LA, left atrium; SAS, subaortic stenosis.

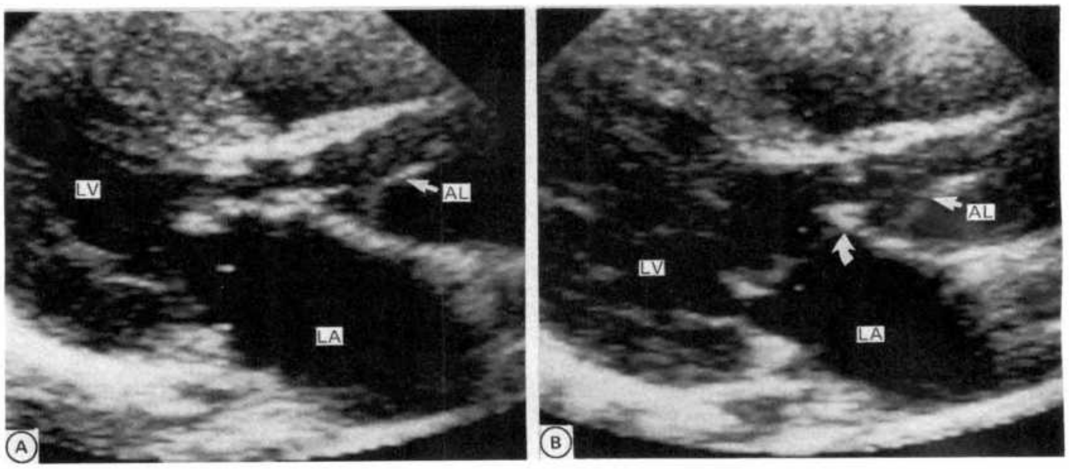

Figure 3 Cross sectional echocardiograms (parasternal long axis views) in a patient with short segment subaortic narrowing and mitral valve involvement. (A) In diastole the obstruction in the left ventricular outflow tract was separate from the aortic valve leaflets but attached to the anterior mitral leaflet. (B) In systole the anterior mitral valve leaflet was pulled anteriorly at the site of attachment of the subaortic obstruction (curved arrow). AL, aortic valve leaflets; LV, left ventricle; LA, left atrium.

and out of the plane of the parasternal short axis section very quickly because of heart movement during the cardiac cycle; frame by frame analysis was necessary to assess it adequately. A localised ridge that did not affect the mitral or aortic valves was the most common type of subaortic stenosis; it was present in 37 (65%) patients (fig 1). Mitral valve (fig 3) or aortic valve (fig 4) involvement was confined to patients with short segment narrowing and was not seen in any patient aged less than 3 years (fig 1). After that age the aortic or mitral valve or both, were often affected (10/34 (30%)) in patients with short segment narrowing and in (10/40 (25%)) the entire group (fig 1). All the patients in whom subaortic stenosis was diagnosed after infancy who had associated coarctation or interruption of the aortic arch had undergone previous repair of the arch abnormality (figs 1 and 5).

There was long segment narrowing in seven (12%) patients (fig 1). The youngest two of these had subaortic stenosis diagnosed at 10 and 16 months of age and each had coarctation of the aorta without a ventricular septal defect. The five others were aged 5 to 13 years at diagnosis (fig 1): one had a ventricular septal defect and another persistence of the arterial duct but there were otherwise no additional abnormalities in these patients.

There were three patients in whom a posteriorly displaced infundibular septum was complicated by an additional discrete subaortic lesion (fig 1). All of these had aortic arch anomalies (two coarctation, one interruption). The patient with interruption of the aortic arch developed long segment narrowing in infancy after neonatal repair of the arch and ventricular septal defect closure, whereas the remaining two patients developed localised narrowing that was first apparent beyond infancy (fig 1). During the period of the study there were 12 additional patients who had malalignment ventricular septal defects with posterior deviation of the infundibular septum into the left ventricular outflow tract who did not develop additional discrete subaortic obstruction.

One infant had unusual redundant tissue obstructing the left ventricular outflow tract. Necropsy confirmed that this was fibrous tissue arising from the membranous septum.

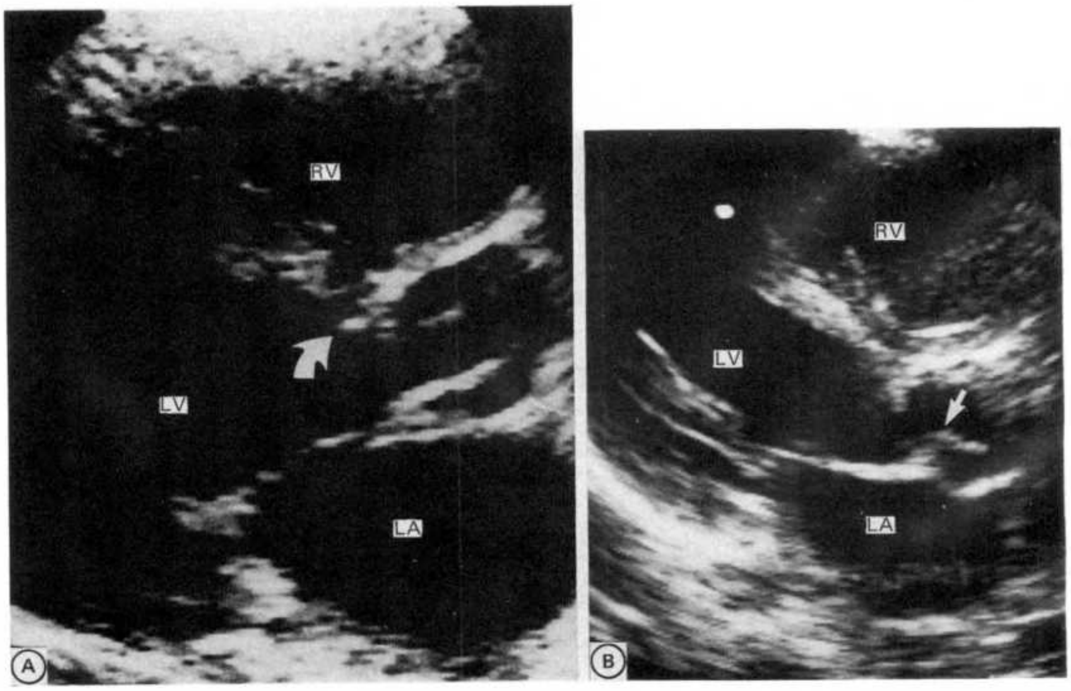

Figure 4 Systolic parasternal long axis views in different patients with tethering of (A) right coronary and (B) left coronary cusps of the aortic valve to the adjacent short segment subaortic ridge (arrows). RV, right ventricle. See legend to fig 3 for other abbreviations.

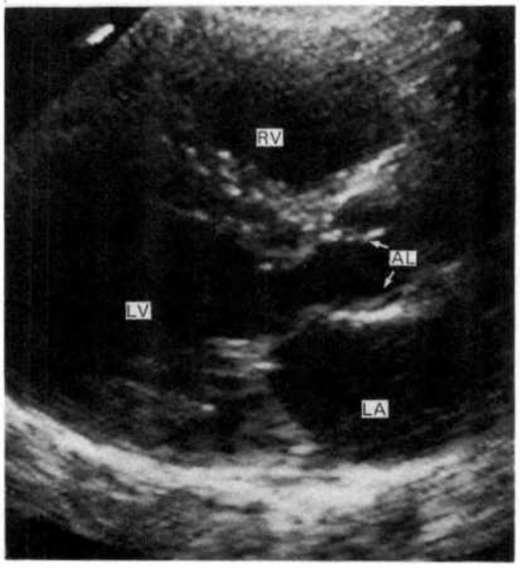

Figure 5 Parasternal long axis view in a 10 year old boy with long segment subaortic stenosis. See legend to fig 2 for abbreviations.

SEQUENTIAL CHANGES

Echocardiograms had been performed before the diagnosis of subaortic stenosis in nine (16%) patients. In six of these the left ventricular outflow tract was considered to be "normal" at the time of the first echocardiogram, performed in infancy in each case (fig 6). Each of these infants had clinically evident associated cardiac anomalies. Careful retrospective review with frame by frame analysis showed subtle irregularity in the location in the left ventricular outflow tract in two of these patients, suggesting that very early ridge formation might have been apparent at the initial study (undertaken at 3 and 4 weeks of age respectively). Careful retrospective review of the echocardiograms recorded in infancy in the remaining four patients considered to have a "normal" left ventricular outflow tract did not show any abnormality (fig 7).

The three patients with posterior displacement of the infundibular septum into the left ventricular outflow tract who subsequently developed additional discrete subaortic stenosis (fig 6) have been described above.

Ten of the 14 patients who had further echocardiograms after the diagnosis of subaortic stenosis had persistence of short segment narrowing (fig 6). In one infant who had undergone coarctation repair there was rapid evolution of short segment to long segment narrowing (figs 6 and 8). The long segment narrowing was confirmed at operation. Acquired valve involvement was seen in four patients. Short segment narrowing evolved to include tethering of the mitral valve (two patients) or aortic valve (two patients, fig 6). Ages at diagnosis of new valve involvement ranged from 5 to 16 years (fig 6).

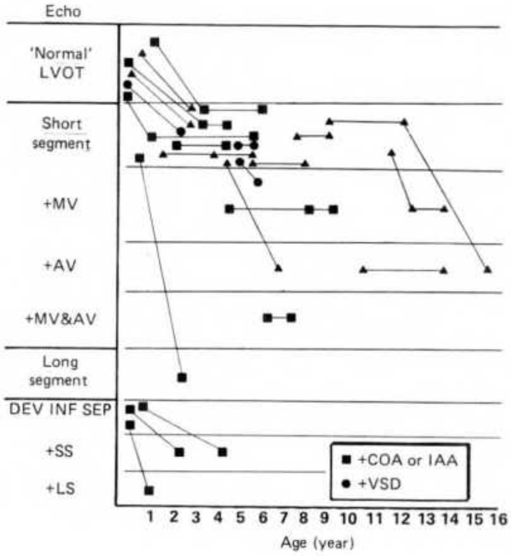

Figure 6 Echocardiographic appearances of subaortic obstruction in patients who had more than one study. LVOT, left ventricular outflow tract. See legends to figs 1–3 for other abbreviations and symbols.

In three patients with repaired coarctation, short segment narrowing with aortic or mitral valve involvement was diagnosed at 3–5 years of age (fig 1). In another, long segment narrowing was diagnosed at 16 months of age (fig 1). Subaortic stenosis had not been diagnosed at the time of coarctation repair in infancy in any of these patients but, because echocardiograms from that time were not available, serial changes in the shape of the left ventricular outflow tract could not be described.

Discussion

CLASSIFICATION OF SUBAORTIC STENOSIS

At least nine mechanisms for subaortic obstruction have been described.[11] Almost all cases, however, are examples of "fibrous diaphragm" or "fibromuscular" narrowing if posterior displacement of the infundibular septum and hypertrophic cardiomyopathy are excluded.[11] These categories inevitably overlap because "fibrous diaphragm" refers to narrowing over a short but unspecified length whereas "fibromuscular" narrowing occurs over a longer but variable length. Our classification of subaortic lesions into short segment, long segment, and displaced infundibular septum with additional localised narrowing was based purely on echocardiographic appearances without inferring the composition of the subaortic tissue. In one infant we described an unusual appearance as "aberrant tissue"; this was shown at necropsy to be an extension of fibrous tissue from the membranous septum. The distinction between short segment narrowing and long segment narrowing was based on previous work[10] but was nevertheless arbitrary. In practice, there was little difficulty classifying the appearances in individual cases. "Fixed subaortic stenosis" may be the preferred term to encompass these lesions.[8]

PROGRESSION OF SUBAORTIC STENOSIS

Subaortic stenosis may cause progressively more severe obstruction of the left ventricular outflow tract.[7] Significant obstruction has developed even in the absence of a systolic pressure difference between left ventricle and aorta at a previous catheterisation,[3,7] showing that lesions can present as an "acquired" disorder that increases in haemodynamic severity, presumably when there is a pre-existing anatomical substrate.[3] Most patients in these studies[3,7] were first seen before cross sectional echocardiography became available. We used echocardiography in an attempt to

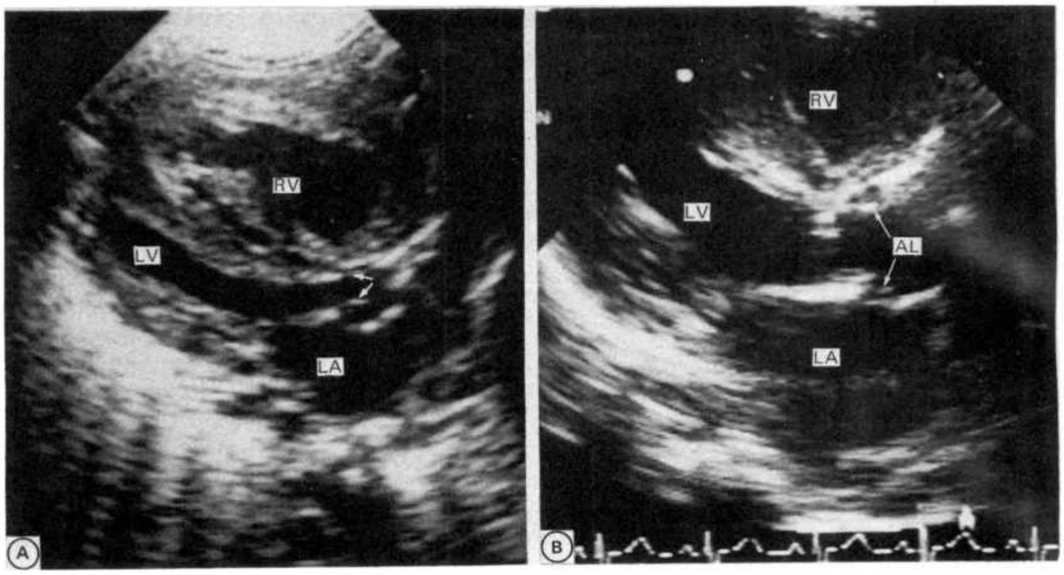

Figure 7 (A) Parasternal long axis view in systole in a neonate with coarctation of the aorta. The left ventricle was small but there was no evidence of obstruction in the left ventricular outflow tract. The arrows indicate the aortic valve leaflets. (B) Parasternal long axis view in systole in the same patient at age 3 years. Short segment subaortic stenosis had developed. See legends to figs 3 and 4 for abbreviations.

assess the anatomical range of fixed subaortic stenosis and the nature of its progression in a consecutive unselected series of infants and children.

Our data confirmed that short segment narrowing is by far the most common form of fixed subaortic stenosis and that most cases are associated with congenital heart defects, typically ventricular septal defect and obstructive lesions of the left heart. The association between obstructive lesions of the left heart and fixed subaortic stenosis was recognised as long ago as 1963.[12] Persistence of the left sided superior vena cava was a notable feature, which we found in nine (16%) of our patients. We previously noted a similar association between persistence of the left superior vena cava and supravalvar mitral stenosis (6/16 patients, 38%) but not in patients with cor triatriatum (0/6 patients) or with congenital mitral stenosis without a supravalvar membrane (1/16 patients, 6%).[13 14] This suggests that persistence of the left superior vena cava with consequent enlargement of the coronary sinus may restrict left ventricular filling during prenatal life and that the diminished flow may contribute to the development of the various "downstream" fixed obstructive lesions.

The classification of the fixed subaortic lesion did not change in most infants and children in this study, but follow up before surgical procedures on the left ventricular outflow tract was short (maximum six years). Short segment narrowing, however, caused progressively more important obstruction of the left ventricular outflow tract.[3]

Tethering of the mitral valve or aortic valve or both, was not seen before the age of 3 years but developed or was present in most children (7/13, 54%) who had at least one serial assessment at age 5 years or more. The development of aortic regurgitation when fixed subaortic stenosis is present is almost certainly the result both of tethering of the aortic valve and the trauma to the valve from the turbulent ejection jet during left ventricular systole.[10]

In rare cases, however, long segment subaortic stenosis can rapidly develop in infancy. An infant in whom severe long segment narrowing developed within four months of repair of aortic coarctation has been reported. The left ventricular outflow tract had been considered

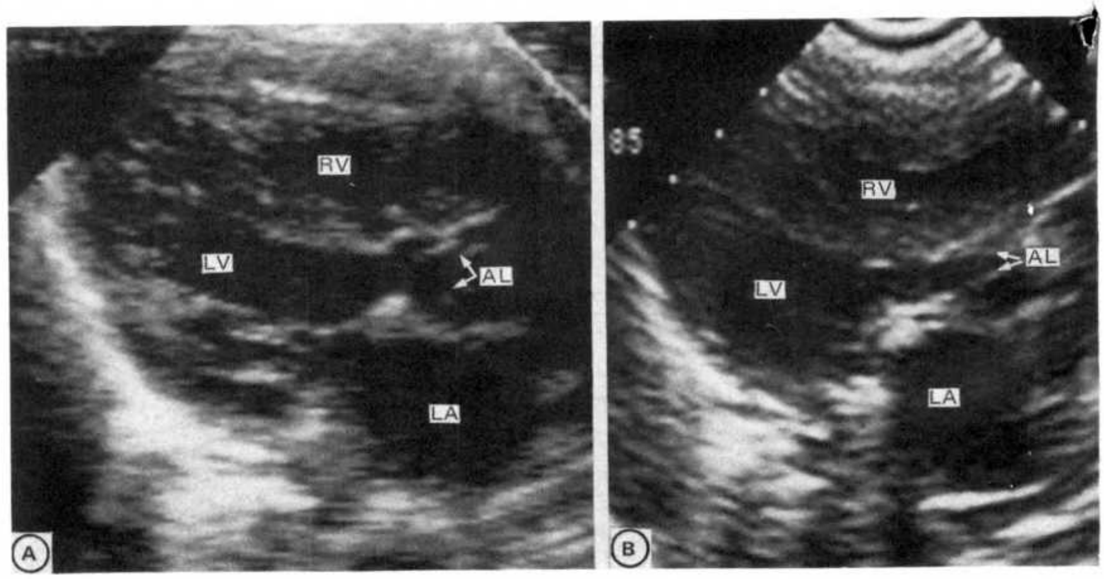

Figure 8 (A) Parasternal long axis view in systole in an infant aged 6 months, showing short segment subaortic narrowing. Coarctation was repaired at that time. (B) Parasternal long axis view in the same patient aged 20 months. Long segment subaortic stenosis had evolved and dysplasia of the mitral valve was evident. See legends to figs 3 and 4 for abbreviations.

normal on initial echocardiographic and angiocardiographic assessment at age 7 weeks.[15] In the two patients in this study who followed a similar course after repair of coarctation, the "substrate" in the left ventricular outflow tract was short segment narrowing in one and displacement of the infundibular septum in the other. In two additional children, we saw the development of a localised ridge superimposed on a posteriorly displaced infundibular septum after repair of coarctation in infancy.

Consequently, the potential for changes in form as well as for progression in haemodynamic severity of left ventricular outflow tract obstruction exists. Reports of long segment subaortic stenosis described patients who were much older than those in our series.[10 16 17] Perhaps short segment narrowing would have evolved into long segment narrowing in more of our patients during a longer prospective follow up. The term "transitional" was used to describe a form of subaortic stenosis intermediate between "discrete" and "tunnel" types in a study that included young adults.[18]

In infants with coarctation or interruption of the aortic arch the left ventricular outflow tract is narrow even in the absence of an aortic valve abnormality or of a malalignment ventricular septal defect with posterior deviation of the infundibular septum. Reduced aortic valve diameter and increased mitral aortic separation were identified in a pathological study of patients with isolated subaortic stenosis.[18] It was suggested that the altered flow characteristics in a narrow and elongated left ventricular outflow tract during early heart development could cause embryonic cells near the crest of the ventricular septum to accumulate and later differentiate into a ridge or band of tissue.[18] When subaortic stenosis occurs in association with a ventricular septal defect but without other abnormality, the obstruction in the left ventricular outflow tract is typically at the lower margin of a perimembranous defect.[11] Maximum turbulence at this site in the presence of a left to right shunt through the ventricular septal defect might explain this and also the tendency for subaortic stenosis to be especially associated with malalignment ventricular septal defects in which there is anterior deviation of the outlet septum[19 20] where the flow disturbance at the lower margin of a perimembranous defect is likely to be even greater.

CLINICAL IMPLICATIONS

We studied infants with clinically evident congenital heart defects. Subaortic stenosis was seen in six young children who had had an apparently normal left ventricular outflow tract in infancy; this accords with the contention that fixed subaortic stenosis is a lesion acquired because of flow disturbance in the left ventricular outflow tract.[18 21] A review of the echocardiographic studies to examine the left ventricular outflow tract showed that very early "ridge" development in the outflow tract may have been present in two patients. A similar appearance was described in an infant, but it was not stated whether subaortic stenosis developed subsequently.[7]

The sequential changes that we saw emphasise the need for careful serial echocardiographic assessment of the left ventricular outflow tract in infants with other obstructive lesions of the left heart, especially if physical signs of left ventricular outflow tract obstruction might be obscured by coexisting abnormalities. Similarly, patients about to undergo ventricular septal defect closure should have a detailed echocardiographic assessment to detect possible incipient subaortic stenosis because surgical removal of any fibrous tissue with the potential to cause subsequent left ventricular outflow tract obstruction is advisable, even when this is only an "echodense area at the crest of the ventricular septum" seen during preoperative echocardiographic assessment.[20]

When fixed subaortic stenosis is "isolated", the likelihood of increasing left ventricular outflow tract obstruction, tethering of the aortic and mitral valves, and the risk of endocarditis argue in favour of early operation.[8 9] However, recurrent or residual postoperative left ventricular outflow tract obstruction is an important complication of operation,[21] and some children with fixed subaortic stenosis do not develop increasingly severe left ventricular outflow tract obstruction or other complications during follow up for many years. Surgical results are probably satisfactory for at least a decade provided the obstruction of left ventricular outflow tract is effectively relieved at the initial operation.[22] The postoperative prognosis of patients with short segment subaortic stenosis was better than those with long segment narrowing.[17] It might therefore be argued that indications for operation should include evidence of important or increasing left ventricular outflow tract obstruction, the development of mitral or aortic valve tethering, or evidence of possible transition from short segment to long segment narrowing on serial studies. Certainly, serial echocardiographic assessment of the left ventricular outflow tract is mandatory for medical management.

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PLANTS IN CARDIOLOGY

Veratrum alkaloids

The *Veratrum* species (Liliaceae) contain over 20 alkaloids with important cardiovascular, neuromuscular, and respiratory actions. They lower the blood pressure by an unusual mechanism first elucidated in 1867 by A von Bezold. Stimulation of vagal afferent fibres in the left ventricle causes the vasomotor centre to reset homoeostatic control at a lower level and to reduce the peripheral vascular resistance through the sympathetic nervous system. When pure alkaloids became available they were shown by A E Doyle and F H Smirk (*British Heart Journal* 1953;**15**:439–49) and by others to reduce considerably the blood pressure in hypertensive patients. But toxicity, especially nausea and vomiting also caused by vagal action, made treatment difficult and their use stopped despite their attractive vasodilator mode of action. *Veratrum* was used in eclampsia before its pharmacology was studied. It had been given for mania and epilepsy early in the nineteenth century and prompted Dr P de L Baker of Eufala, Alabama, to prescribe *Veratrum viride*, the American or green hellebore, with success in 1859 for a lady with eclamptic fits. This was well before the association between eclampsia and hypertension was recognised. The plant and its alkaloids were used with good effect in toxaemia of pregnancy and eclampsia for the next 100 years.

Veratrum viride Ait. Bentley R, Trimen H. *Medicinal plants*. vol 4. London: Churchill, 1880: 286.

The *Veratrum* species are handsome perennial plants with large pleated leaves and tall spikes of flowers—well worth growing in the garden. The two European species, *V album* and *V nigrum*, are common on alpine meadows. There are 43 other species, the best known being *V viride* and *V sabadilla*. The alkaloids come from the rhizome and root, or occasionally from the seed. Their common name, from antiquity, is hellebore but they are quite different from the genus *Helleborus*—the Christmas and Lenten roses. *Veratrum* has always been known as a highly poisonous plant causing vomiting, substernal constriction, faintness with a weak pulse, convulsions, and death. In 1985 a Frenchman made wine from it, believing it to be gentian, and developed complete atrioventricular block. It is also known as a strong teratogen; ewes that eat it can have lambs with a central eye.

Other medicinal members of the Lily family include those that contain cardiac glycosides, such as squill (*Drimia maritima*) and lily of the valley (*Convallaria majalis*). Colchicine is found in the meadow saffron ("autumn crocus") *Colchicum autumnale* while sisal *Agave sisalana* provides the starting material for steroid synthesis.

A HOLLMAN

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Phrenic nerve injury in infants and children undergoing cardiac surgery

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Abstract

Fifty infants and 50 children less than 15 years undergoing palliative or corrective cardiac surgery in the Brompton Hospital between March and October 1988 had direct percutaneous stimulation of the phrenic nerve before and after operation. Ten patients, six under 1 year of age and four over, developed unilateral phrenic nerve injury. In those aged less than 1 year recovery after operation was prolonged because their diaphragmatic palsy made it difficult to wean them from the ventilator. Older children had symptoms but their rate of recovery did not seem to be affected by the phrenic nerve injury. Phrenic nerve damage was no more frequent after a lateral thoracotomy than after a median sternotomy. There was no significant association with the type of operation performed, the experience of the surgeon, the use of bypass or topical ice, the duration of bypass, circulatory arrest or aortic cross clamping, or the age of the patient at the time of operation. In patients who had cardiopulmonary bypass the risk of injury was significantly higher in those who had undergone previous operation. The 10% frequency of phrenic nerve injury determined in this prospective study was higher than that seen in earlier retrospective reports.

Direct percutaneous stimulation of the phrenic nerve can be used at the bedside in infants and children to facilitate early and accurate diagnosis of phrenic nerve palsy, and the results may influence early management.

Phrenic nerve injury is a known complication of cardiac surgery[1 2] that results in paralysis of the diaphragm and impairs respiratory function. It can prolong the postoperative course. Such injury was found in 0·5% to 2·2% of paediatric patients in retrospective studies.[3–7] In these studies the criteria for diagnosis were difficulty in weaning from a ventilator, a raised hemidiaphragm on chest radiographs, or decreased or paradoxical diaphragmatic movement on fluoroscopy. Percutaneous phrenic nerve stimulation is an established technique for assessing nerve function.[8–11] The technique was used in two small groups of adult patients to measure the incidence of phrenic nerve injury after cardiac surgery; incidences of 8% and 11% were obtained.[12 13] This non-invasive technique was modified for use in infants and children in the Brompton Hospital in a preliminary study[14] and normal values have also been established (in preparation). We performed a prospective study of 100 infants and children undergoing cardiac surgery to determine the frequency and predisposing factors contributing to phrenic nerve injury.

Patients and methods

The study was approved by the hospital medical ethics committee and parental consent was obtained. We studied 100 unselected infants and children undergoing palliative or corrective surgery for congenital heart disease in the Brompton Hospital between March and October 1988. Figure 1 shows their age distribution which ranged from 1 day to 14·5 years (median age 15 months). Table 1 summarises the diagnoses at operation, the type of operation performed, and the number of children in each group. To assess phrenic nerve involvement phrenic nerve latency was measured before operation and as soon as possible after operation when they were no longer on muscle relaxants. Because the test could be performed while the patients were still on the ventilator, they were studied within 72 hours of operation. Twenty three children had had a previous operation and two of them had pre-existing phrenic nerve injury with a prolonged phrenic nerve latency though both were symptom free when tested before the present operation. Measurements of normal phrenic nerve latency and diaphragmatic electromyograms during preoperative testing showed that all the remaining patients had normal phrenic nerve function.

METHODS

Each phrenic nerve was stimulated percutaneously by bipolar electrodes at the pos-

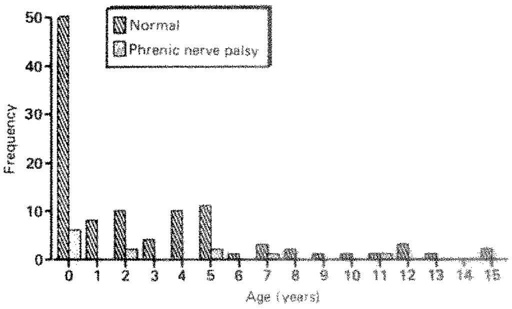

Figure 1 Histogram showing age distribution of 100 patients in the study.

Table 1 Classification of diagnoses and operation

Diagnosis	*Operation type*	*No*	*Total*
Transposition of great arteries	Arterial switch	9	19
	Mustard procedure	4	
	Rastelli procedure	1	
	Redo switch	2	
	Coarct repair, PA band	2	
	VSD closure	1	
Tetralogy of Fallot	Total correction	8	10
	Shunt	2	
Pulmonary atresia	Rastelli procedure	1	8
	Shunt	7	
Tricuspid atresia	Fontan procedure	4	5
	Shunt	1	
Total anomalous pulm venous connection	Correction	2	2
Ventricular septal defect	VSD closure	10	17
	and relief RVOTO	5	
	and ASD closure	2	
Atrial septal defect	ASD closure	7	7
Atrioventricular septal defect	AVSD repair	2	3
	Mitral valve repair	1	
Patent ductus arteriosus	PDA ligation	6	6
Left ventricular outflow obstruction	Coarct repair	6	9
	Mitral valve repair	2	
	Muscle resection	1	
Right ventricular outflow obstruction	Pulmonary valvotomy	3	4
	Muscle resection	1	
Complex heart disease	Enlargement VSD	2	10
	Shunt	5	
	Coarct repair, PA band	2	
	PA band	1	
Total			100

ASD, atrial septal defect; AVSD, atrioventricular septal defect; Coarct, coarctation of the aorta; PA band, pulmonary artery band; PDA, persistent ductus arteriosus; RVOTO, right ventricular outflow tract obstruction; VSD, ventricular septal defect.

terior border of the sternomastoid at the level of the upper border of the thyroid cartilage.[8-11] Square wave stimuli with a supramaximal current (6–45 mA) that lasted 0·1–0·2 ms were applied to each nerve at a frequency of 1 Hz. The ipsilateral diaphragmatic compound muscle action potential was detected by surface electrodes placed in the seventh intercostal space at the anterior axillary line. This electromyogram was amplified and displayed on the screen of an oscilloscope and recorded photographically. The earth electrode was placed just below the xiphisternum to avoid disturbing the surgical dressings (figs 2 and 3). Occasional excitation of the brachial plexus was seen because the phrenic nerve lies close to the nerve trunks at the point of stimulation.

The conduction time of the phrenic nerve was measured as the terminal latency between the stimulation artefact and the onset of the diaphragmatic muscle action potential. This gives a reliable assessment of phrenic nerve function.[8 10] Phrenic nerve injury was diagnosed if the nerve latency was increased to more than twice the preoperative value or if no detectable diaphragmatic electromyographic or mechanical response was obtained despite supramaximal stimulation on repeated testing (fig 4). We used fluoroscopy to detect paradoxical or reduced movement of the diaphragm in this latter group of patients to confirm the diagnosis of diaphragm paralysis.

We tested the association of phrenic nerve injury with dichotomous factors by the χ^2 test with Yates's correction. The Mann-Whitney test was used for other factors.

Results

Ten patients (10%) had abnormal unilateral phrenic nerve latencies after operation. In seven of these patients the phrenic nerve latency was at least twice the preoperative value, while in the remaining three no activity was detected on the diaphragmatic electromyogram. Figure 5 shows the relation between preoperative and postoperative phrenic nerve latencies. Phrenic nerve injury occurred on the right side in four patients and on the left in six patients. In six of the 10 patients cardiopulmonary bypass had been performed via median sternotomies. In four the operation was performed via right or left lateral thoracotomies without bypass. After a lateral thoracotomy phrenic nerve palsy occurred on the same side as the incision. All the ten patients had basal atelectasis or a raised

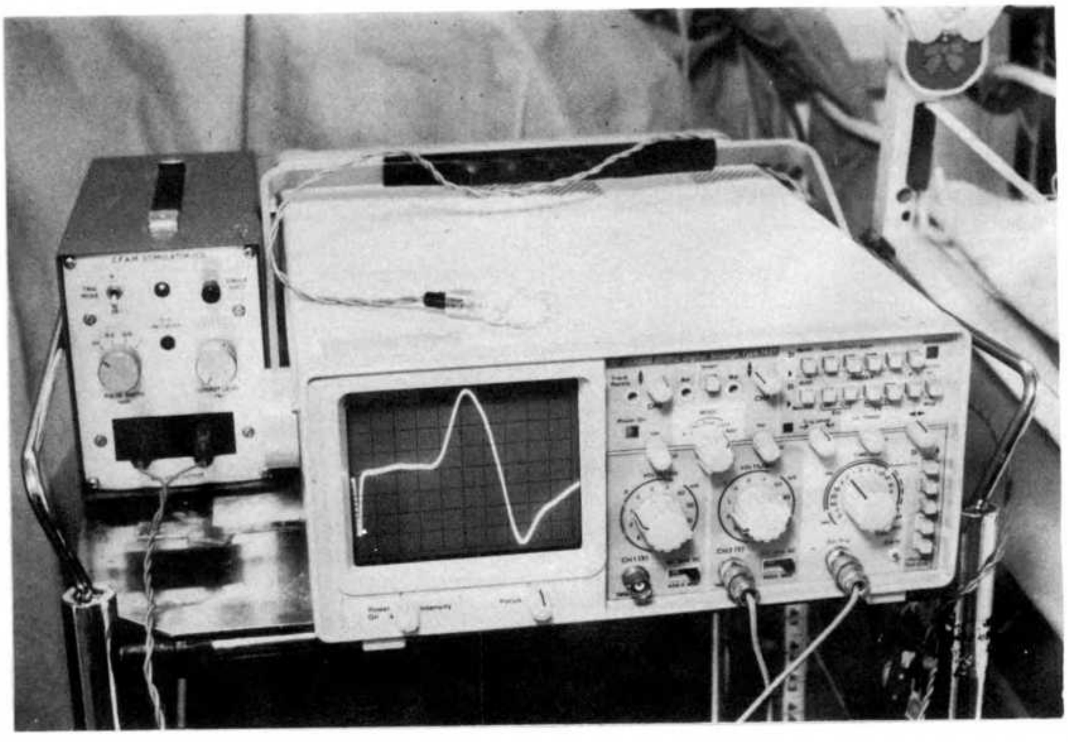

Figure 2 Equipment used to test phrenic nerve: nerve stimulator (left), bipolar electrode modified for use in paediatric patients, and oscilloscope for recording the electromyogram.

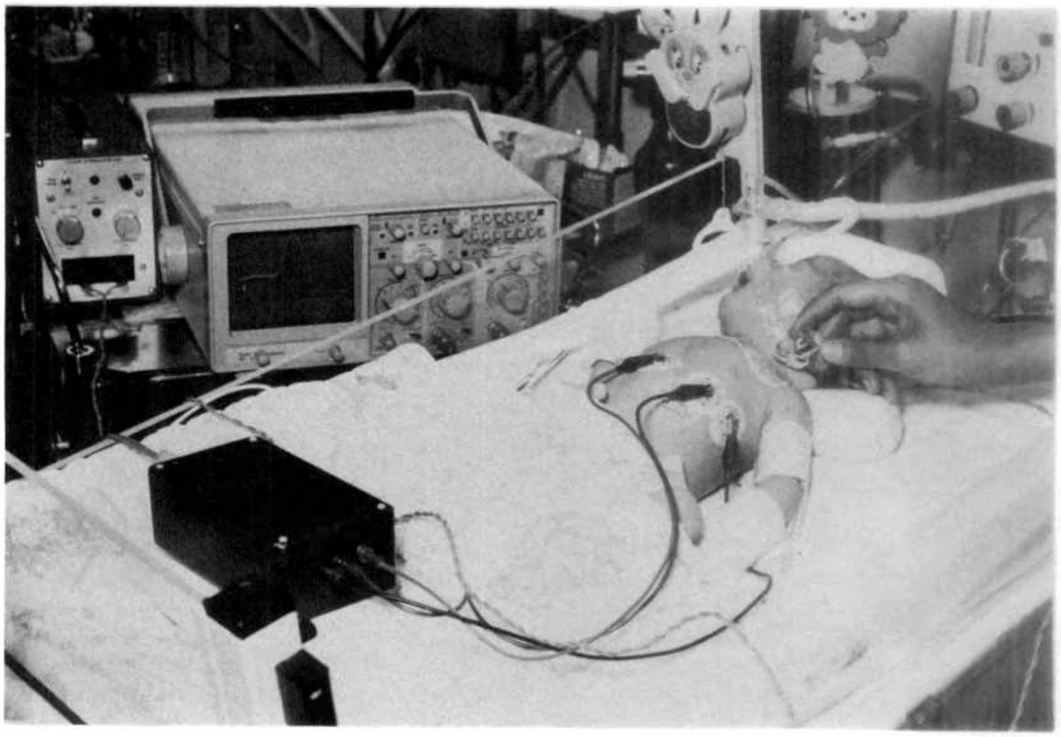

Figure 3 Postoperative test on a ventilated patient showing location of the surface electrodes and position for percutaneous stimulation of phrenic nerve.

hemidiaphragm on chest *x* ray (fig 6), though this was often not evident while the patient was on positive pressure ventilation.

Table 2 summarises data on the affected patients and their outcomes. All the children who required a prolonged period of ventilation were less than 1 year old, except for patient 8 who was failing to thrive and weighed 6·8 kg at the age of 2, and patient 6 who was ventilated for other reasons and in whom there was evidence of recovery of phrenic nerve function. Four of the neonates subsequently required plication of the affected diaphragm to facilitate extubation, after many attempts to wean them from ventilatory support. Because repeated electrophysiological testing could not be used to predict temporary or permanent damage (as nerve recovery is slow), plication was performed on clinical grounds. Patients 3 and 8 did not have plication but they were nursed in negative pressure tanks because various other complications precluded further operation. Four of the ten patients eventually died, three as a direct result of respiratory failure caused by diaphragmatic impairment while the remaining patient died from other surgical complications.

We assessed many factors in our attempt to determine associated causes of phrenic nerve injury. These included the underlying diagnosis and type of operation (bypass or non-bypass), the duration of bypass, aortic cross clamping or circulatory arrest, the temperature to which the patient was cooled, the use of topical ice, the experience of the surgeon (con-

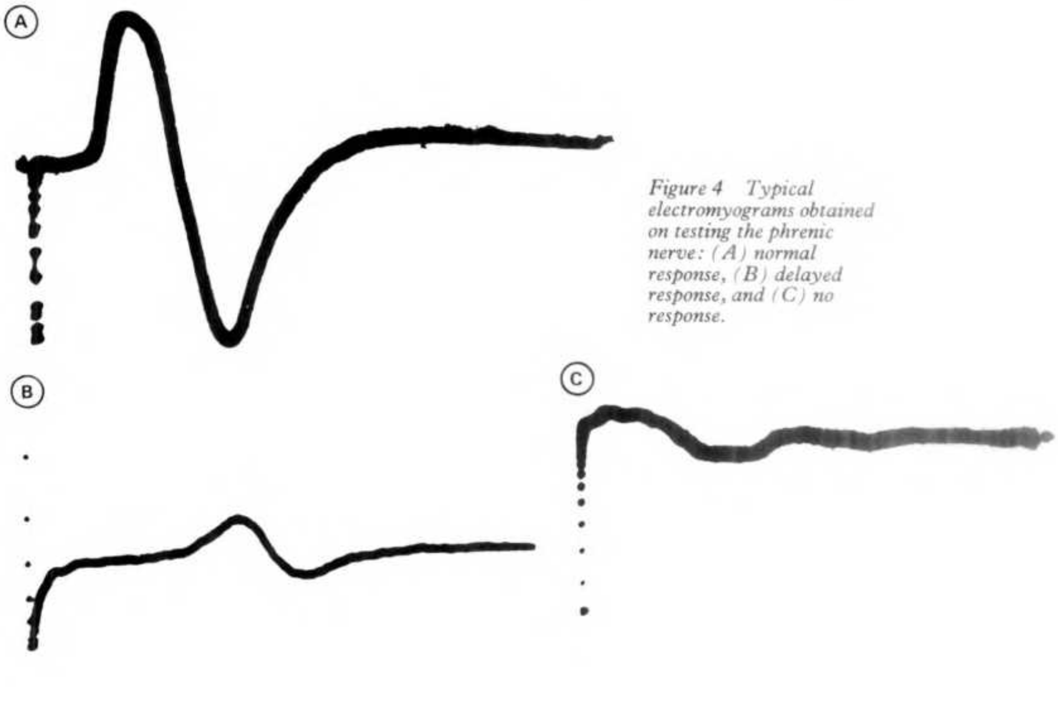

Figure 4 Typical electromyograms obtained on testing the phrenic nerve: (A) normal response, (B) delayed response, and (C) no response.

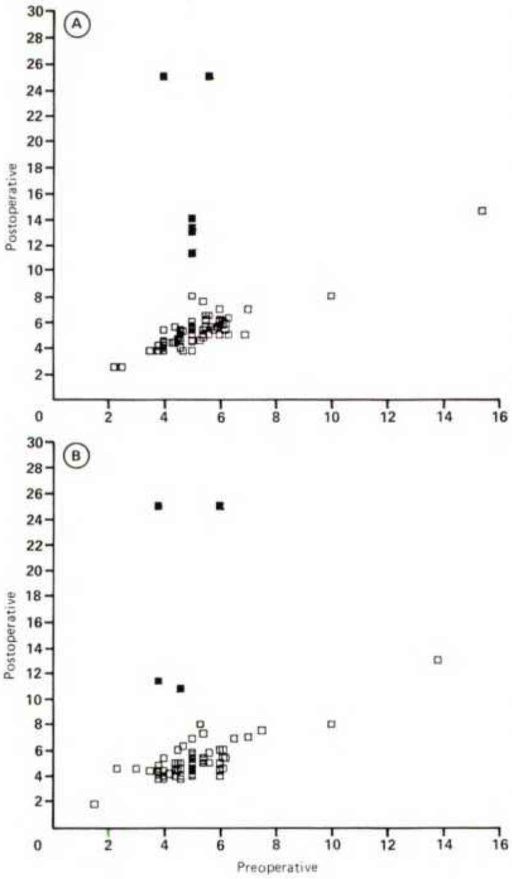

Figure 5 Scattergram of the relation between preoperative and postoperative phrenic nerve latency ((A) left, (B) right). Phrenic nerve injury was defined as postoperative latency of more than twice the preoperative value. Absent responses were assigned a maximum latency of 25 ms.

sultant or non-consultant), the presence of previous operations, the incision site, and the age at operation. There was a significant association with previous surgery ($p < 0{\cdot}05$) in only the 68 bypass cases; however, the phrenic nerve injury after the subsequent operation was not always on the same side as the previous thoracotomy. No other significant associated factor was found though there might have been a marginal risk associated with the experience of the surgeon; consultant surgeons had a smaller risk ($p = 0{\cdot}1$) than with senior registrars or registrars.

Discussion

We found that the incidence of phrenic nerve injury in paediatric cardiac surgery was higher than was previously reported in retrospective studies[3–7] but similar to small studies based on phrenic nerve stimulation in adults.[12,13] This may be because phrenic nerve damage was underestimated in older children in retrospective studies where the selection was based on a prolonged postoperative course or difficulty in weaning from the ventilator. We found that though phrenic nerve paralysis causes severe respiratory embarrassment in neonates it seems to cause fewer clinical or physiological abnormalities in children who are more than 1 year old, unless there is associated weakness of other respiratory muscles. Respiratory muscle physiology in the older child seems to be similar to that in adults, who cope with unilateral or bilateral diaphragm paralysis with only a few symptoms.[15,16] Retrospective studies also based their diagnoses on the presence of a raised hemidiaphragm on the chest *x* ray or paradoxical movement of the diaphragm on ultrasound scanning or fluoroscopy. These methods of diagnosis may be unreliable while the patient is on positive pressure ventilation or where there is bilateral phrenic nerve palsy and the true incidence of the condition may be underestimated.[6,17,18]

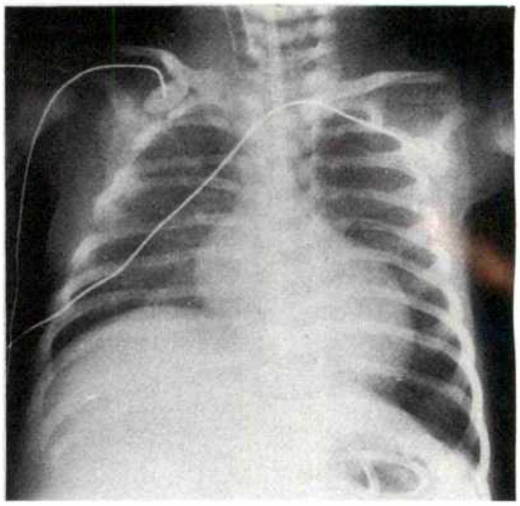

Figure 6 Chest x ray showing raised hemidiaphragm seen in phrenic nerve injury.

Infants with phrenic nerve injury have an increased morbidity and mortality from the resulting diaphragmatic palsy.[3,5,6] They require a significantly longer period of ventilation because of episodes of acute respiratory distress. This is because of major differences in the respiratory physiology in infants.[19,20] Contrac-

Table 2 Data on patients with phrenic nerve injury

Case No	Diagnosis	Operation	Age	Side	Ventilation	Plication
1	TGA, VSD, Coarct	PA band, Coarct repair	2 days	L	IPPV 24 days	+
2	PA, VSD	Left shunt	1 day	L	IPPV 14 days	+
3	TGA	Mustard	3·5 mnth	L	IPPV 36 days, CNEP 30 days	–
4	TGA, PS, Switch	Redo RVOT	2 yr	L	IPPV 1 day	–
5	MS	MV repair	11·5 yr	R	IPPV 12 hours	–
6	TA, PA band	Fontan	5·5 yr	R	IPPV 19 days	–
7	TGA	Switch	3 days	L	IPPV 14 days	–
8	TGA, VSD, Coarct rep, PA band	Switch	2·3 yr	L	IPPV 27 days, CNEP 60 days	–
9	TGA, PS	Right shunt	1 day	R	IPPV 28 days	+
10	TGA, PS	Right shunt	2 days	R	IPPV 51 days	+

Coarct, coarctation of the aorta; CNEP, continuous negative extrathoracic pressure ventilation; IPPV, intermittent positive pressure ventilation; MS, mitral stenosis; MV, mitral valve; PA, pulmonary atresia; PA band, pulmonary artery band; PS, pulmonary stenosis; RVOTO, right ventricular outflow tract obstruction; TGA, transposition of the great arteries; VSD, ventricular septal defect.

tion of the diaphragm is less efficient in infants because they have a circular thorax, horizontal orientation of the ribs, and greater compliance of the rib cage. In normal breathing in adults the diaphragm stabilises the thorax during inspiration.[21,22] This effect is especially important in infants because they have weaker intercostal muscles. In supine adults the abdominal contents press on the diaphragm and reduce the functional residual capacity by 15%.[23] This expected reduction in functional residual capacity in the supine infants is aggravated in phrenic nerve injury where the loss of the hydraulic piston effect and the raising of the flaccid diaphragm reduce the parenchymal lung volume even more. This increases atelectasis and mediastinal shift so much that both factors interfere with respiration in both the affected and normal lung.[24] Younger infants are also more susceptible to fatigue of the diaphragm because of the smaller proportion of type I (slow twitch, high oxidative) muscle fibres.[25]

Previous studies have implicated "frostbite injury" from the topical slush used for myocardial preservation in bypass surgery as the cause of phrenic nerve injury[17,18] and this hypothesis was confirmed by experiments in dogs.[26,27] Several workers suggested that the use of various insulation pads reduced the incidence.[28-30] We, however, found that phrenic nerve damage was as common in non-bypass surgery in which neither cold cardioplegic solutions nor topical ice was used. There was also no association with the cooling temperature or duration of bypass, suggesting that other factors, for example direct or indirect surgical trauma, may be equally important.

Secondary procedures after previous thoracotomies can increase the incidence of phrenic nerve paralysis.[5,6] The presence of fibrous adhesions and scarring from previous operation would obscure the anatomy of the pericardium and phrenic nerve and make them more liable to injury. We also found an association between phrenic nerve injury and previous operation but only when bypass cases were considered separately. The reason for this is unclear but it could be that a combination of more demanding bypass surgery and scarring from previous operations contributed to the higher risk. A closer examination of the data in references 5 and 6 bears this out because the association of phrenic nerve injury with previous thoracotomies was found only among patients who had open heart surgical procedures.

There was no obvious association between phrenic nerve injury and the age at operation, the type of surgery, or the incision site. The duration of bypass, aortic cross clamping or circulatory arrest, and the temperature to which the patient was cooled were not found to be significant factors. There may have been too few patients affected in this study to show an association.

Phrenic nerve paralysis can result in many complications including episodes of aspiration, respiratory infections, cardiac arrhythmias, or cardiorespiratory arrests and death.[1] Various workers have suggested different methods of management to overcome this problem, recommending repair of the transected nerve,[31] long term ventilation with or without tracheostomy,[32] and early[3] or late[4-6] plication of the diaphragm. We found that plication of the diaphragm reduced complications from prolonged ventilation because it allowed earlier extubation. The decision to plicate could be taken with greater assurance and less delay because phrenic nerve injury was accurately assessed by this technique. It did not, however, seem to improve survival rates in the patients with phrenic nerve injury and persistent diaphragmatic palsy.

Phrenic nerve conduction studies can be easily performed at the bedside with the equipment and technique described above. Early and accurate detection of phrenic nerve injury is possible while the patient is ventilated, before clinical or radiological evidence of diaphragmatic dysfunction. Phrenic nerve injury is a common and important complication of cardiac surgery in infants and children that increases morbidity and mortality. Early detection of injury identifies the infants who may require early diaphragmatic plication, thus preventing an unnecessary and prolonged course of ventilation and the associated complications.

We thank Mr V Aber for help with statistical analysis of the data

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CASE REPORTS

Prenatal diagnosis of a complex fetal cardiac malformation associated with asplenia

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Abstract

A case of a complex fetal heart malformation with left isomerism, a "right sided" double outlet ventricle, and aortic isthmus stenosis combined with asplenia was diagnosed by ultrasonography at 26 weeks' gestation. The pregnancy was terminated at the request of the parents in the 27th week of gestation. Because the prognosis for a fetus with cardiosplenic syndromes depends mainly on the severity of the cardiac abnormality cases of visceral heterotaxy should be classified according to the predominant feature, the heart malformation.

Congenital heart disease is sometimes associated with anomalies of the situs of the visceral organs (visceral heterotaxy). The term cardiosplenic syndrome is used to describe the combination of a heart defect with asplenia[1] or the so-called "polysplenia syndrome".[2] Absence of the spleen is usually associated with right isomerism (two morphologically right atrial appendages), bilaterally trilobed (morphologically right) lungs and bronchial trees, and a central liver ("asplenia syndrome"). The cardiac abnormalities include total anomalous pulmonary venous return, atrioventricular septal defect, double inlet ventricle, discordant ventriculoarterial connection, and pulmonary stenosis or atresia.[3 4] The inferior vena cava and abdominal aorta run together right or left of the spine, and the aorta is located posteriorly.

Polysplenia, or multiple small spleens, is often combined with left isomerism (two morphological left atrial appendages) and bilateral bilobed (morphological left) lungs and bronchi. In about 70% of cases the inferior vena cava is absent and replaced by the azygos vein. In polysplenia possible cardiac defects show a wide spectrum of atrial and atrioventricular septal defects; double outlet right ventricle or transposition of the great arteries are rare.[2] In both asplenia and polysplenia other visceral organs are commonly affected.

Prenatal diagnosis of the unusual combination of left isomerism with asplenia has already been reported.[5] We report the prenatal diagnosis of left isomerism, a "right sided" double outlet ventricle, and aortic isthmus stenosis.

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Case report

A 32 year old woman (gravida 1) was referred for ultrasound examination because of fetal bradycardia during a non-stress test. Ultrasound examination (Toshiba Sonolayer SSA-250A, Toshiba Medical Systems) showed one fetus with biometric data appropriate for the gestational age of 26 weeks. The heart rate was 60 to 70 beats/min, fetal ascites was visible, as was cardiac failure.

ECHOCARDIOGRAPHIC EXAMINATION

The fetal heart seemed to be displaced to the right more than normal and the apex seemed to be on the left. The descending aorta ran to the right of the spine. The four-chamber view showed two extremely dilated atria with a big primum atrial septal defect and two small ventricles with hypertrophic walls (Fig 1a and b). We also found a small ventricular septal defect of the hypertrophic

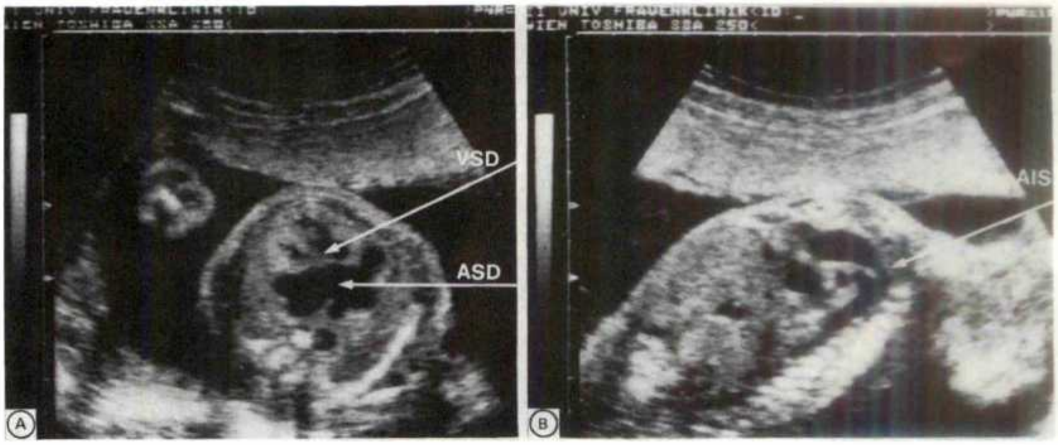

Figure 1 Echocardiograms showing (A) a big atrial septal defect (ASD), a small ventricular septal defect (VSD), and hypertrophic ventricular walls in four chamber view and (B) stenosis of the aortic isthmus (AIS) with dilatation proximally and distally in longitudinal section.

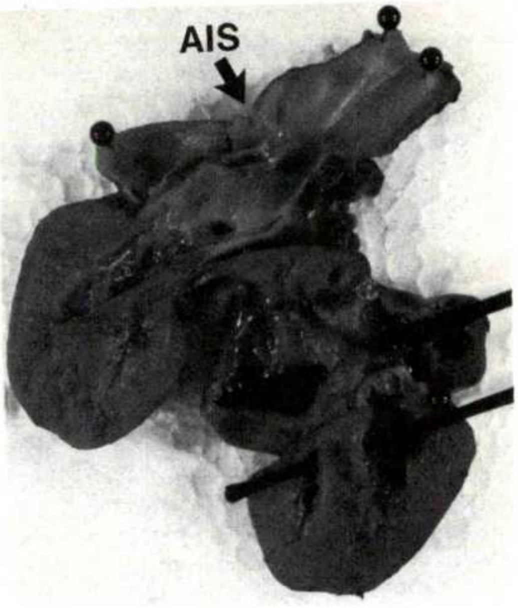

Figure 2 Necropsy of the fetal heart. Upper stylet marks the big atrial septal defect, the lower the ventricular septal defect, and the arrow indicates the aortic isthmus stenosis (AIS). Both great vessels (aorta and pulmonary trunk) arise from the right sided main chamber.

interventricular septum. Two separate atrioventricular valves were seen. Left of the larger main chamber a smaller ventricle was visualised with an atrioventricular valve inserted more apically (morphological right ventricle on the left side). This small chamber was connected to the left sided atrium. A vessel thought to be the superior vena cava and the hepatic veins drained into this atrium. A dilated venous abdominal vessel (azygos vein) that ran left of the spine and showed no connection with the hepatic veins drained into the superior vena cava and into this left sided atrium. The right sided larger ventricle seemed to be morphologically left because of the insertion of its atrioventricular valve. Both the dilated pulmonary trunk and the aorta arose from this ventricle. The aorta showed a stenosis of the isthmus with proximal and distal dilatation. The descending aorta ran right of the spine and in front of the azygos vein, which, however, ran left of the spine. M mode investigation repeated several times during the examination ruled out complete heart block.

Placental biopsy showed a normal male karyotype. The parents were told about the prognosis by the paediatrician and they requested a termination. This was performed in week 27 of gestation.

FINDINGS AT NECROPSY

Postmortem examination showed a male infant. The spleen was absent. The lungs were bilaterally bilobed with bilateral hyparterial bronchial trees. The superior and inferior mesenteric arteries were connected to a single vessel. The abdominal aorta ran on the right of the spine and the abdominal venous vessel on the left. The heart was displaced to the right with its apex pointing to the left. Inspection showed that both atria had typical left atrial appendages (fig 2). The pulmonary veins drained into the right sided atrium. The superior vena cava, which took up the azygos vein, was connected to the left sided atrium into which the hepatic veins also drained directly. A big atrial septal defect and a small subvalvar ventricular septal defect were found. There were two separate atrioventricular valves. The walls of the right and left ventricles could not be morphologically distinguished because of hypertrophy. Both the pulmonary trunk and the aortic arch arose from the right sided ventricle. The aortic valve was in continuity with the atrioventricular valve of the right ventricle. On both sides of the stenosis at the isthmus the aorta was dilated.

Discussion

The term "cardiosplenic syndrome" describes complex congenital malformations of the heart and spleen in which there is a tendency toward symmetrical development of organs and organ systems that are usually asymmetrical.[6] Because many other organs including the lungs, intestines, kidneys, and venous system may be affected it is more accurate to use the term visceral heterotaxy to describe this syndrome.

The anatomical details of the fetal spleen, lungs, and intestines cannot be reliably displayed by current ultrasound methods. Therefore prenatal diagnosis of such malformations in combination with the absence or multiplication of the spleen and cardiac abnormalities must focus on examination of the heart. In fetal echocardiography, as in anatomical studies, sequential analysis of the chambers and connections of the heart is based on morphological characteristics.[7–9] Usually the morphological right structures are found on the right side (situs solitus). In situs inversus, the morphological right structures are found on the left side. The term isomerism is used to describe the situation when paired organs such as the atria (or lungs) have identical morphological characteristics.

Classic terminology combines absence of the spleen with right isomerism. The prognosis is generally considered to be poor because transposition of the great arteries with pulmonary stenosis or atresia and total anomalous pulmonary venous drainage are often present.[10]

Polysplenia typically is associated with left isomerism and azygos vein continuation. The overall outcome is thought to be better than for asplenia and the accompanying cardiac defects show a wide range of severity.[4 10]

Cases of right isomerism (no spleen expected) with detectable splenic tissue as well as left isomerism with asplenia (polysplenia expected) do not belong to either group.[11–14] These cases, however, were diagnosed at necropsy.

Stewart *et al* were the first to report two cases of left atrial isomerism diagnosed prenatally by fetal echocardiography in which necropsy showed asplenia.[5] We report prenatal diagnosis of left isomerism, a double outlet "right sided" ventricle, and stenosis of the aortic isthmus associated with absence of the spleen. Because of several "crossover" cases, "asplenia" and "polysplenia" are regarded as imperfect terms to describe cardiosplenic syndromes. The combined heart lesions of our fetus fit perfectly into a classification based on the atrial arrangement according to atrial appendage morphology.

In left isomerism (two morphological left atrial appendages) azygos vein continuation is typical.[13,15] Also two morphologically left (that is, bilobed) lungs and bronchial trees were present.[2,4,14] Atrial septal defect and ventricular septal defect are often found, as in our case. A double outlet ventricle is encountered in about 9–20%.[4,10] The association of isomerism of the left atrial appendages with aortic outflow obstruction at different levels has been reported[13]; however, this is a rare combination. The malformations typical of right isomerism such as anomalous pulmonary venous drainage, transposition of the great arteries, and pulmonary stenosis or atresia were not present in our case. Fetal bradycardia is usually due to complete heart block[16] which is often present in cases with left isomerism.[17] However, in our case severe sinus bradycardia followed by ascites showed that the fetus was about to die. After consulting the paediatrician the parents decided to request termination of the pregnancy, because surgical correction of the heart defect was regarded as impossible.

Prenatal evaluation of splenic disorders is unreliable. However, even complex and uncommon cases of cardiosplenic syndromes can be diagnosed prenatally by sequential morphological echocardiographic analysis of the heart and great vessels, as shown in our case. The prognosis of a fetus with a malformation of this kind depends on the severity of cardiac abnormality. Therefore, cardiosplenic syndromes should be classified according to the most important clinical feature—the heart malformation.

We thank Dr Patricia Stewart, Erasmus University, Dijkzigt, Rotterdam, for her invaluable advice.

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Salmonella: a rare cause of subacute effusive-constrictive pericarditis

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Abstract

A 36 year old woman had emergency pericardectomy because of subacute effusive-constrictive pericarditis. The pericardial fluid and tissue culture showed that this was caused by infection with *Salmonella enteritidis*. Cardiac involvement with salmonella does not usually present in such an aggressive manner and it has not previously been reported to cause this rare type of cardiac constriction.

Case report

A 36 year old woman was admitted with an illness that had been progressive over the previous two months. She was unwell, anuric, icteric, and tachypnoeic at rest, with intense orthopnoea. She was afebrile but had signs of severe cardiac constriction with a sinus tachycardia of 120 beats per minute, a low volume pulse, and pulsus paradoxus was seen over a range of 20 mm Hg. Her jugular venous pressure was 10 cm above the sternal angle and she had sacral oedema, gross hepatomegaly, and reduced air entry to both lung bases. There was a pericardial friction rub and mild mitral regurgitation. Her electrocardiogram showed low voltage complexes with T wave flattening laterally and inversion in I and aVL. A chest *x* ray confirmed bilateral pleural effusions and showed considerable globular "cardiomegaly". Echocardiography showed a pericardial effusion of moderate size with biventricular collapse in diastole. The most striking abnormality was the very thick, echodense pericardium. Doppler echocardiography showed mitral valve prolapse with mild mitral regurgitation. Her biochemical profile was abnormal. Before transfer to the Freeman Hospital, she had mild hepatic dysfunction but on arrival her liver function tests were disturbed. The prothrombin time was twice the control value and pre-renal failure had developed.

Over the previous month she had been treated with various antibiotics for a presumed chest infection and had then been admitted to her local hospital for investigation of continuing breathlessness. She was found to have a pericardial effusion of moderate size containing fronds but had no clinical or echocardiographic evidence of cardiac tamponade. The effusion was presumed to be viral in aetiology and benign in nature. After a period of relative stability, her condition progressively deteriorated over a two week period. A normochromic normocytic anaemia (92 g/l) developed and the erythrocyte sedimentation rate rose to 70 mm in the first hour (Westergren). Recurrent pleural effusions required drainage of a total of four litres of clear fluid. All samples were bacteriologically sterile and showed no evidence of infection with tubercle.

Soon after transfer to this hospital, emergency pericardectomy was performed via a left anterolateral thoracotomy. The pericardium was considerably thickened, inflamed and oedematous, and enclosed a moderate purulent effusion. On the visceral aspect there was a purulent exudate with associated fibrin. Histological examination showed that the pericardium was 4 mm thick and was composed of a fibrous layer showing evidence of non-specific chronic inflammatory changes with a perivascular distribution. *Salmonella enteritidis* was cultured from blood, pericardial fluid, and pericardial samples. The organism was sensitive to ciprofloxacin and this treatment was continued for 17 days. Titres to *Salmonella typhi* and *S paratyphi* were negative, as were stool cultures. No primary source of salmonella could be confirmed.

The patient's subsequent course was satisfactory apart from transient hyponatraemia and pyrexia. After hospital discharge, she returned to normal activities. Her serum alkaline phosphatase concentration remained raised but otherwise the biochemical and radiological variables returned to normal. Echocardiography showed persistent mitral regurgitation.

Discussion

Acute pericarditis is commonly associated with an insignificant pericardial effusion. It may progress to chronic pericardial constriction but rarely to subacute effusive-constrictive pericarditis where a tense effusion is contained within a markedly thickened pericardium. With the widespread use of antibiotics and the decline of tuberculosis it is rare now for constrictive pericarditis to result from bacterial infection.[1-3] Effusive-constrictive pericarditis was first described by Burchell in 1954[4] and its haemodynamic impact was later defined.[5] Relief of the tamponade by aspiration of the effusion does not improve the clinical condition because of the associated constriction.[6] Most cases of effusive-constrictive pericarditis are idiopathic in origin but there are reports of it occurring with tuberculosis,

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viral, bacterial, and amoebic infections; in uraemia, rheumatoid arthritis, and carcinoma; and after radiation and thoracic trauma.[6–8] It has not previously been described as a complication of salmonella infection, although Bird's postmortem report in 1969 has some similar features.[9] The rapid progression to tamponade in our patient may be due to the nature of the causative organism. Effusive-constrictive pericarditis usually progresses to non-effusive chronic constriction over the course of a year.[5]

There are more than 1700 different serological types of salmonella but most are primarily animal parasites with little human pathogenicity. Salmonella infections can take one of two forms: firstly, typhoid fever which is due to *Salmonella typhi* or *S paratyphi* and can be complicated by endocarditis or myocarditis,[10] and secondly, *S enteritidis* and some other strains which can give symptoms and signs of food poisoning after transmission by undercooked meat of contaminated animals or contamination of other food stuffs by a human carrier. Metastatic spread from the gastrointestinal tract may result in pyrexia of unknown origin, meningitis, or osteomyelitis. It is uncommon for the heart to be secondarily affected but endocarditis and myocarditis have been described.[11] The pericardium is rarely involved in salmonella infections. Pericarditis was first recorded in association with typhoid fever in 1844[12] and there are few previous reports of pericarditis in non-typhoidal syndromes in published reports[10 13] after the original description in 1936.[14] It tends to occur in older patients and is often associated with a purulent effusion from which the organism may be cultured.[15] This is the first report of *Salmonella enteritidis* as the causative organism.

Subacute effusive-constrictive pericarditis due to infection with salmonella has not previously been reported. This case report highlights the potential for this unusual organism to have a highly aggressive presentation. The purulent pericardial exudate rapidly led to the development of prominent pericardial thickening and constriction requiring urgent surgical intervention to relieve cardiac tamponade. It seems prudent therefore to consider diagnostic aspiration of pericardial effusions that do not resolve promptly. Bacteriological testing would then identify unusual organisms whose malignant course might be prevented by early and appropriate treatment.

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BRITISH CARDIAC SOCIETY NEWSLETTER

We have news from the European Society of Cardiology that will by now be known to most of our members. After the untimely death in January of Attilio Reale, Michel Bertrand (who was President Elect) has been appointed Acting President until his own term of office is due to begin in 1994. Professor Bertrand is well known in Britain as in the rest of Europe. We wish him well. We are also delighted to report that in 1995 the European Society of Cardiology will almost certainly be coming to Birmingham, so that the British Cardiac Society will have the privilege of being hosts to a major European meeting for the first time.

Readers may remember that the joint British Cardiac Society/Royal College of Physicians Audit Committee has at present three major projects. The visits between district general hospitals, the national confidential enquiry into cardiac catheter complications (CECCC), and the survey of delays to treatment in acute myocardial infarction are all going well and their scope is being widened as had previously been planned. Nick Brooks who is chairman of the committee is now requesting that members of the society should let him know of other initiatives that are felt to be important. Some suggestions have been made, but before new priorities are decided we are anxious to consider as many appropriate ideas as possible. Please write either direct to Nick Brooks or to us at the society.

David de Bono has written about the confidential enquiry on catheter complications. Cardiac catheterisation and coronary angiography are fundamental to modern cardiology: good equipment and skilled operators have made them safe procedures, but complications do sometimes occur. In August 1990 the Joint Audit Committee of the British Cardiac Society and the Royal College of Physicians of London set up a pilot study of five cardiac centres with the aim of pooling information about catheter laboratory complications, so that the lessons learned could be shared and common factors, in particular complications, would be recognised. This initiative was reported briefly in the newsletter of December 1990. The pilot study has been very successful and it is now intended to extend the scheme to all United Kingdom catheter laboratories. The scheme is being coordinated from the Department of Cardiology in the University of Leicester, and individual units will have been approached by the time this newsletter appears. The data required from each centre are very modest, and a monthly newsletter from Leicester will keep participants informed of progress. David de Bono is anxious to stress that all information will be treated as strictly confidential. We hope that every centre will respond with enthusiasm.

We also wish to draw attention to another important survey coming from Leicester, this one organised by Peter Hubner. Since 1988, the British Cardiovascular Intervention Society has undertaken a survey of all adult and paediatric intervention procedures (angiography and balloon dilatations). The report on the second survey from 1989 is soon to be published, and the third enquiry was sent out for completion by the end of January. By the time of writing (mid-March), 21 adult National Health Service units, two private units, and 10 paediatric units had replied. A total of 34 units had not. In these days of audit, information technology, and competitive costings, this type of information should be readily available to support a department's activities and budgets. The replies from all units are needed before the 1990 audit can be analysed. By now perhaps the response will be complete. If not, we hear a threat to publish a list of non-responders. . .

Peter Hubner has agreed to extend the scope of his survey on behalf of the British Cardiac Society, though the additional scheme will be serviced for us by the British Cardiovascular Intervention Society. We wish to give every trainee cardiologist the opportunity to register all procedures he or she undertakes—angiography, pacemaker implants, electrophysiology studies, as well as intervention procedures. The British Pacing and Electrophysiology Group have indicated their approval. This will be a voluntary scheme, but registration on a monthly basis will aid accurate counting, and will lend credence to claims relating to practical experience—particularly in connection with applications for posts. Will this be supported? Our surgical colleagues have long had a similar scheme and find it helpful.

We have news on the composition of the Cardiac Technicians Committee which is being set up under the chairmanship of Duncan Dymond. The committee will consist of one nominated council member from each of the five affiliated working groups. So far individuals have been nominated from three of the groups; those from echocardiography and pacing and electrophysiology are awaited. The vice chairman of the Society of Cardiological Technicians will also be on the committee as will the President of the British Cardiac Society. Duncan Dymond will represent the British Cardiovascular Intervention Society, Shakeel Qureshi will represent the Paediatric Cardiology Group, and Jane Flint will represent the Nuclear Cardiology Group. Although the final composition of the committee has not been formulated, the principal aims of the committee will be to seek ways of improving the training and of raising the entry standards of cardiological technicians in the United Kingdom (which should result in further improvements in their status), and to forge closer links with the Society of Cardiological Technicians. These have not been as strong as many would wish, and much of the responsibility for this must rest with the cardiologists.

We will end on a lighter note. Do all consultant cardiologists in district hospitals now have a fax machine within their homes? Students of Latin will feel this question should begin with the word "num" (and those not well versed in the classics can contact us in confidence for an explanation). The advantages are considerable. We have all agonised on whether a telephone description of an electrocardiogram represents ventricular tachycardia or something more benign, and perhaps more recently we have hoped for inspiration when the telephone evidence seems inadequate on whether or not thrombolysis is indicated. Should we go in to the hospital at 4 am knowing that it will not then be worth returning home for breakfast? Is it not better to have an electrocardiogram waiting by the telephone when we wake up? The cost of a fax machine is now less than that of a single ampoule of one of the thrombolytic agents. Is it not worth it for the sake of better patient care and more confident and better rested consultants?

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NOTICES

1991

A course on the use of **New Devices for the Cardiac and Peripheral Vascular Laboratories** will be held in Orlando, Florida, on 1 to 3 July: Shadyside Hospital, New Devices Technology Workshop, 5230 Centre Avenue, Pittsburgh, PA 15232, USA (412 623-1051).

Angioplasty 1991: A Live Demonstration Course presented by the San Francisco Heart Institute will be held in San Francisco on 12 to 15 August: Steve Lugon, Course Coordinator, San Francisco Heart Institute at Seton Medical Center, 1900 Sullivan Avenue, Daly City, CA 94015, USA (Fax: 415-755-7315; Tel: 415-991-6355).

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May.

1993

The XVII World Congress on Diseases of the Chest sponsored by the International Academy of Chest Physicians and Surgeons will be held in Amsterdam on 13 to 18 June: ACCP, Division of Education, 3300 Dundee Road, Northbrook, IL 60062-2348, USA (Fax 708-498-5460; Tel: 708-498-1400).

CORRECTION

St Cyres lecture. Endothelium in control *A H Henderson* (March issue, volume 65: pages 116–25)—The author has asked us to point out that reference 142 should have read: Zeiher AM, Drexler H, Wollschläger H, Just H. Modulation of coronary vasomotor tone humans. Circulation 1991;83:391–401